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Chest tightness is relieved with the use of asthma drugs except bronchodilators

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ABSTRACT

Objective: Many patients with a chief complaint of chest tightness are examined in medical facilities, and a lack of diagnosis is not uncommon. We have reported that these patients often include those with chest tightness relieved with bronchodilator use (CTRB) and those with chest tightness relieved with the use of asthma drugs except bronchodilators (CTRAEB). The purpose of this study was to demonstrate the clinical characteristics of the patients with CTRAEB and compare them with data from patients with CTRB. **Methods:** Patients with CTRB ($n = 13$) and CTRAEB ($n = 7$) underwent a bronchodilator test, assessments of airway responsiveness to methacholine, bronchial biopsy, and bronchial lavage under fiberoptic bronchoscopy before receiving treatment. In all, 10 healthy subjects, 11 bronchial biopsy control patients, and 10 asthmatic patients were recruited for comparison. **Results:** Inhalation of a short-acting β_2 -agonist (SABA) increased the forced expiratory volume in one second (FEV_1) by $5.1\% \pm 4.0\%$ in patients with CTRB and by $1.3\% \pm 3.5\%$ in patients with CTRAEB, and the difference was statistically significant ($p = 0.0449$). The bronchial biopsy specimens from the patients with CTRB and CTRAEB exhibited significant increases in T cells ($p < .05$) compared with those of the control subjects. The bronchial responsiveness to methacholine was increased in only a minor portion of patients with CTRB and CTRAEB. **Conclusions:** We hypothesized that the clinical condition of patients with CTRAEB involves chest tightness arising from inflammation alone, and this chest tightness is mostly associated with airway T cells, without constriction of the airways. There is little to distinguish CTRAEB from CTRB aside from the response to bronchodilator treatment. This clinical trial is registered at www.umin.ac.jp (UMIN13994, 13998, and 16741).

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Introduction

Chest tightness is a common symptom of diverse diseases. Many patients with a chief complaint of chest tightness are examined in medical facilities, and although angina, reflux esophagitis, or esophageal candidiasis is often diagnosed, a lack of diagnosis is not uncommon. We have reported that these patients often include those with chest tightness relieved with bronchodilator use (CTRB) and those with chest tightness relieved with the use of asthma drugs except bronchodilators (CTRAEB) [1].

Whitney and coworkers reported on three patients who presented with CTRB. Because bronchodilators are effective, clinical conditions presenting as CTRB are thought to be a subtype of asthma and are called “chest pain variant asthma (CPVA)”, and several articles in the medical literature have addressed this disease [1–6]. No clear diagnostic criteria for CPVA have been established, but it should be defined as CTRB without characteristic bronchial asthma (BA) exacerbation [1]. CPVA is common in our experience [2].

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The typical clinical presentation of CTRB is tightness centered on the retrosternal region or heaviness of the chest, and the tightness may sometimes radiate to the back, head, or right and left chest regions. CTRB and CTREB have very similar clinical presentations in our past reports [1] and are difficult to diagnose based on medical history and the usual examinations; currently, it is thought that pharmacologic stress testing is the most useful type of diagnostic testing. CTRB is diagnosed by noting an improvement in chest tightness after administration of a β_2 -agonist, whereas CTREB is diagnosed by noting chest tightness improvement after administration of a leukotriene receptor antagonist (LTRA), thromboxane synthetase inhibitor (TXSI), histamine 1 receptor antagonist (H1RA), theophylline, or corticosteroid. In our previous experience, most patients with CTREB respond to an LTRA, followed by a high rate of response to a TXSI [1,7,8].

Patients with classic BA often experience chest tightness [9]. In the Global Initiative for Asthma (GINA) guidelines, chest tightness is listed as a symptom of asthma [10]. In our experience, asthma patients have the potential to experience CTRB and/or CTREB [1].

The purpose of the present study was to demonstrate the clinical characteristics, pathophysiology, pathology, and medical treatment of patients with CTREB without BA and to compare data of patients with CTREB with data from patients with CTRB.

Methods

Study oversight

We conducted this prospective study between 2014 and 2018 at the Toyama Prefectural Central Hospital. After patient screening and baseline assessments were performed, the participants underwent several examinations and treatment. This study conformed to the Declaration of Helsinki, and it was approved by the ethics committee of the Toyama Prefectural Central Hospital (numbers 2010–4 and 4903). This clinical trial is registered at www.umin.ac.jp (UMIN13994, 13998, and 16741).

Subjects

In this study, patients who complained primarily of chest tightness were diagnosed with a flow chart, as shown in Figure 1. These patients had not been diagnosed with BA, with the exception of childhood asthma, before the first examination. These patients had not presented with characteristic BA attacks and had normal breath sounds. We excluded patients with cardiac diseases, such as angina, and infectious diseases, such as

pleuritis, diagnosed by chest computed tomography scanning, stress electrocardiogram, and blood work assessments. In addition, we also performed a nitroglycerin test for patients with suspected angina as needed.

CTRB was diagnosed by noting an improvement in chest tightness after inhalation of a short-acting β_2 -agonist (SABA, 0.03 mg procaterol hydrochloride) or administration of a long-acting β_2 -agonist (2 mg/day tulobuterol patch).

For the patients with a negative response to the β_2 -agonist, a proton pump inhibitor (PPI, 20 mg/day vonoprazan) was administered for 1 week, and patients were monitored for any improvement in symptoms. In addition, we excluded patients with gastric and esophageal disease, such as gastric ulcer, reflux esophagitis and eosinophilic esophagitis, diagnosed by esophagogastroduodenoscopy. The patients with a positive response to the PPI were diagnosed as having reflux esophagitis.

Patients with a negative response to the PPI were successively administered a LTRA (10 mg/day montelukast sodium), a TXSI (400 mg/day ozagrel hydrochloride), and a H1RA (10 mg/day olopatadine hydrochloride) for 1 week each; drug administration was stopped when some improvement in symptoms was noted with any of the medications, and a diagnosis of CTREB was given. We also recruited patients who had residual symptoms after the medications were stopped or patients whose symptoms worsened upon discontinuing the medication in our evaluation.

All of the bronchial-biopsied control subjects had a peripheral small lung tumor (<3 cm in diameter) requiring bronchoscopic examination for diagnosis, no past history of asthma, no respiratory symptoms, and no smoking history.

All of the patients in the asthmatic group had a history of episodic dyspnea, wheezing, and coughing. These patients exhibited at least 15% reversibility of forced expiratory volume in one second (FEV₁) after inhalation of a SABA (0.03 mg procaterol hydrochloride). Their symptoms were well or fairly controlled by treatment with inhaled fluticasone propionate or fluticasone furoate/vilanterol.

None of the healthy subjects had a past history of asthma, respiratory symptoms, or a smoking history.

All of the subjects provided informed consent after the purpose of the study had been explained.

Clinical and pulmonary function data

All of the patients with CTRB and CTREB underwent measurement of pulmonary function, sputum examination of cell differentials, and measurements of

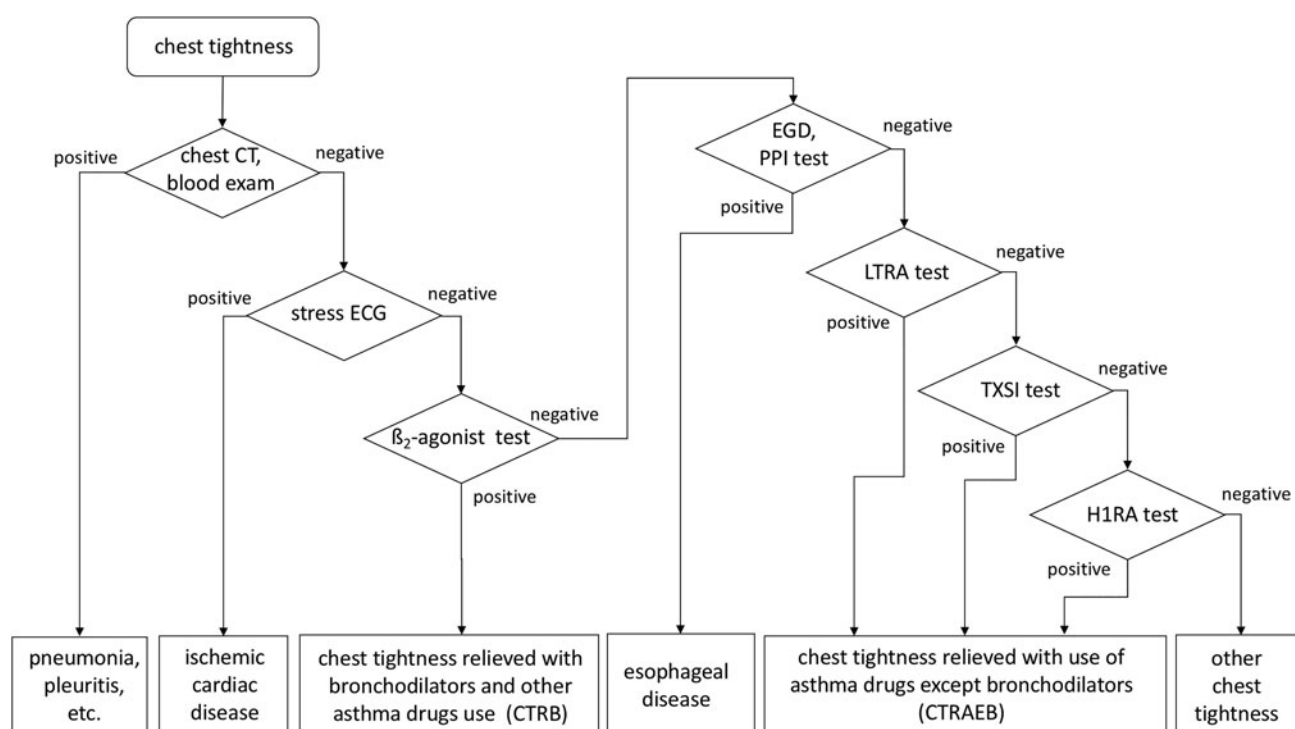


Figure 1. Diagnostic flow chart of patients who complained primarily of chest tightness. CT: computed tomography; ECG: echocardiography; EGD: esophagogastroduodenoscopy; PPI: proton pump inhibitor; LTRA: leukotriene receptor antagonist; TXSI: thromboxane synthetase inhibitor; and H1RA: histamine 1 receptor antagonist.

peripheral blood eosinophil, serum-nonspecific immunoglobulin E (IgE) antibody, and serum-specific IgE antibody levels (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, house dust, cockroach, cat fur, and dog hair) (Uni-CAP[®], Pharmacia Ltd., Milton Keynes, UK). Pulmonary function was measured using a spirometer (DISCOM21 FXIII Chest Co. Ltd., Nagoya, Japan). The highest value of at least three measurements was recorded. The predicted pulmonary function values were extracted from Reference [11].

The greatest levels of chest tightness were evaluated with a numerical rating scale (NRS) [12].

Bronchodilator test

The healthy subjects and patients with CTRB, CTRAEB, and classic BA underwent pulmonary function testing before and 20 min after inhalation of a SABA (0.03 mg procaterol hydrochloride) at the first examination.

Bronchial reactivity

The healthy subjects and patients with CTRB, CTRAEB, and classic BA underwent the methacholine bronchial provocation test to assess airway hyperresponsiveness before bronchial biopsy was performed. Bronchial reactivity was tested with a buffered

methacholine solution using a DeVilbiss no. 646 nebulizer (DeVilbiss Co., Somerset, PA) operated at an airflow of 5 L/min, as previously described [13]. The concentrations of the methacholine solutions were 39, 78, 156, 313, 625, 1250, 2500, 5000, and 10,000 $\mu\text{g/mL}$. The test began with 2 min of inhalation of saline aerosol followed by inhalation of methacholine solutions of successively higher concentrations until a 20% decrease in the FEV_1 relative to the post-saline control value was observed. The FEV_1 was measured with a spirometer (DISCOM21 FXIII) after each challenge and was compared with the value obtained after saline inhalation. Challenge testing was discontinued when the FEV_1 decreased by 20% or more. The provocative concentration of methacholine that caused a 20% decrease in the FEV_1 ($\text{PC}_{20}\text{-FEV}_1$) was calculated by interpolation.

Bronchial biopsies and lavages

All of the patients with CTRB and CTRAEB and the bronchial-biopsied control subjects underwent bronchial biopsy and bronchial lavage using a fiberoptic bronchoscope (BF-P260F, Olympus, Tokyo, Japan) under local anesthesia with lidocaine before treatment. These bronchoscopic procedures were performed between 8 a.m. and 11 a.m. The patients were also

administered midazolam and fentanyl intravenously for sedation before the procedure. The bronchoscope was placed into the right bronchus, and biopsies were obtained from the airway mucosa from both the central and peripheral airways. The central biopsy specimens were collected at a bifurcation of the right upper lobe bronchus and intermediate bronchus, and the peripheral biopsy specimens were obtained from subsegmental airways to bronchioles in the right lower lobe. Two to three biopsies were examined from each airway level using forceps (Radial Jaw 4, Boston Scientific, Galway, Ireland).

Bronchial lavage fluid (BLF) was collected from the middle lobe bronchus using 20 mL of physiological saline solution. Smears for differential leukocyte counts were prepared by May–Grünwald–Giemsa staining.

The control patients underwent bronchial biopsy before peripheral lung tumor biopsy and collection of BLF.

Processing of biopsy specimens

Sections of the biopsy specimens were prepared for light microscopy. For pathological analysis, the specimens were fixed in 10% neutral-buffered formalin for 6 h, embedded in paraffin, sliced into 4- μ m thick sections, and stained with hematoxylin and eosin. The following antibodies were used for immunohistochemical analyses: anti-CD3 (A0452, Dako, High Wycombe, UK), anti-CD4 (1F6, Leica, Newcastle upon Tyne, UK), and anti-CD8 (C8/144B M7103, Dako). Mast cells were detected using a polyclonal antibody against c-cit (A4502, Dako). Macrophages were detected using a polyclonal antibody against CD163 (10D6, Leica).

Light microscopy was performed with Eclipse 80i and DS-Fi1 (Nikon, Tokyo, Japan). The numbers of eosinophils, mast cells, neutrophils, macrophages, and CD3-, CD4-, and CD8-positive cells among epithelial cells and in the submucosa were visually counted by one of the authors, whom was unaware of the clinical findings. The most intact areas of the bronchial epithelium and submucosa were chosen for analyses of mast cells, macrophages, and CD3-, CD4-, and CD8-positive cells. Full visual fields of the bronchial epithelium and submucosa were selected for analyses of eosinophils and neutrophils, which were present at comparatively smaller numbers. Cells located inside the vessels were not counted. The total area of the examined submucosa was calculated by delineating the area of the section using NIS Elements D3.2

(Nikon). The results were expressed as the number of cells per square millimeter of submucosa.

Sputum

All subjects were instructed to cough up sputum. If coughed-up sputum was not collected, expelled sputum was collected during the bronchodilator test.

Treatment

Initially, we treated patients with CTAEAB with effective drugs at diagnosis. If the effect of that drug was insufficient after a month of treatment, then we additionally prescribed another asthma drug except bronchodilators.

We treated the patients with CTRB with 400 μ g per day inhaled fluticasone propionate and procaterol hydrochloride (SABA) as needed. If the effect of inhaled fluticasone propionate was insufficient after a month of treatment, then we additionally prescribed a long-acting β_2 -agonist, LTRA or another asthma drug. If the patient felt that the inhaled fluticasone propionate was ineffective, then we stopped that treatment and alternatively prescribed a long-acting β_2 -agonist, LTRA or another asthma drug.

Statistics

The data are expressed as the means $\pm$ SDs. Between-group differences were determined using Student's t-tests for pulmonary function test data and the Mann–Whitney U-test for the number of cells in bronchial biopsy specimens, bronchial fluid, and sputum. Statistical significance was based on a 95% confidence level ($p < .05$).

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R Commander designed with additional statistical functions frequently used in biostatistics [14].

Results

Clinical data

We recruited 7 patients with CTAEAB, 13 patients with CTRB, 11 control subjects who had undergone bronchial biopsy, 10 patients with classic BA, and 10 healthy subjects. In our previous report, we released data on 11 out of 13 patients with CTRB and 5 out of

Table 1. Clinical characteristics of patients with CTAEAB and CTRB.

	CTAEAB	CTRB
Patient numbers	7	13
Age at diagnosis (years)	42.9 ± 20.2	53.6 ± 20.7
Age at onset (years)	40.9 ± 21.2	48.0 ± 21.5
Male/female	3/4	3/10
Current/former smoker	1/1	0/3
Eosinophils in PB (/μL) ^a	106.1 ± 60.8	179.2 ± 133.1
Serum IgE (U/mL)	130.7 ± 46.0	184.9 ± 269.0
UniCAP-specific IgE ^b positive	3	6
Greatest level of tightness (NRS)	7.1 ± 1.9	8.1 ± 1.7
History of allergic diseases		
AR	5	2
CA	0	1
AD	0	1
Complications		
HT	0	2
LC	0	1
OMI	0	1
RA	0	1
Regions of chest tightness		
Retrosternal tightness	5	7
Retrosternal and left chest tightness	2	0
Tightness from the throat to the entire chest	0	1
Tightness in various parts of the chest	0	1
Retrosternal tightness (with occasional headache)	0	4
Times of chest tightness		
All hours of the day	4	8
A few times a day	2	1
Once a day	0	1
Upon effort	1	3

^aPB, peripheral blood; IgE, immunoglobulin E; AR, allergic rhinitis; CA, childhood asthma; AD, atopic dermatitis; LC, lung cancer;

HT, hypertension; OMI, old myocardial infarction; RA, rheumatoid arthritis.

^bUniCAP-specific IgE, fluoroimmunoanalysis-specific immunoglobulin E.

10 healthy subjects [2]. In this study, all patients with CTAEAB were diagnosed by noting an improvement in chest tightness after LTRA administration.

Among the seven patients with CTAEAB, the average age at diagnosis was 42.9 ± 20.3 years, and the male:female ratio was 3:4 (Table 1). The primary complaints of the patients included retrosternal tightness in six patients and tightness of the left chest in one patient (Table 1).

Among the 13 patients with CTRB, the average age at diagnosis was 53.4 ± 26.9 years, and the male:female ratio was 3:10. The primary complaints of the patients included retrosternal tightness in 11 patients, tightness of various parts of the chest in one, and tightness from the throat throughout the entire chest in one. There was variability in the degree of chest tightness improvement with the inhaled SABA as demonstrated in the questionnaire, ranging from partial to complete improvement.

Among the 11 bronchial-biopsied control patients, the average age at examination was 57.4 ± 15.1 years, and the male:female ratio was 3:8. Among the 10 BA patients, the average age at examination was 47.2 ± 10.8 years, and the male:female ratio was 2:8. Finally, among the 10 healthy subjects, the average age at examination was 29.3 ± 8.3 years, and the male:female ratio was 8:2.

Pulmonary function data

Among the seven patients with CTAEAB, the vital capacity (VC) was 3,491 ± 578 mL, the predicted VC% was 112.3% ± 10.0%, the FEV₁ was 3,063 ± 774 mL, the predicted FEV₁% was 112.5% ± 10.1%, the peak expiratory flow rate (PEF) was 6,661 ± 1,026 mL/s, the predicted PEF% was 76.9% ± 13.0%, and the FEV₁/forced vital capacity (FVC) ratio was 87.1 ± 10.0 on the initial pulmonary function test.

Among the 13 patients with CTRB, the VC was 3,569 ± 1,239 mL, the predicted VC% was 124.9% ± 16.2%, the FEV₁ was 2,864 ± 1,064 mL, the predicted FEV₁% was 124.1% ± 21.2%, the PEF was 5,968 ± 1,847 mL/s, the predicted PEF% was 77.2% ± 14.1%, and the FEV₁/FVC ratio was 80.9 ± 4.8 on the initial pulmonary function test.

No significant difference was found between patients with CTAEAB and CTRB for VC ($p = 0.8506$), FEV₁ ($p = 0.6383$), PEF ($p = 0.2951$), and FEV₁/FVC ratio ($p = 0.1615$) on the initial pulmonary function test.

Bronchodilator test

Among the seven patients with CTAEAB, all patients experienced chest tightness at the first examination

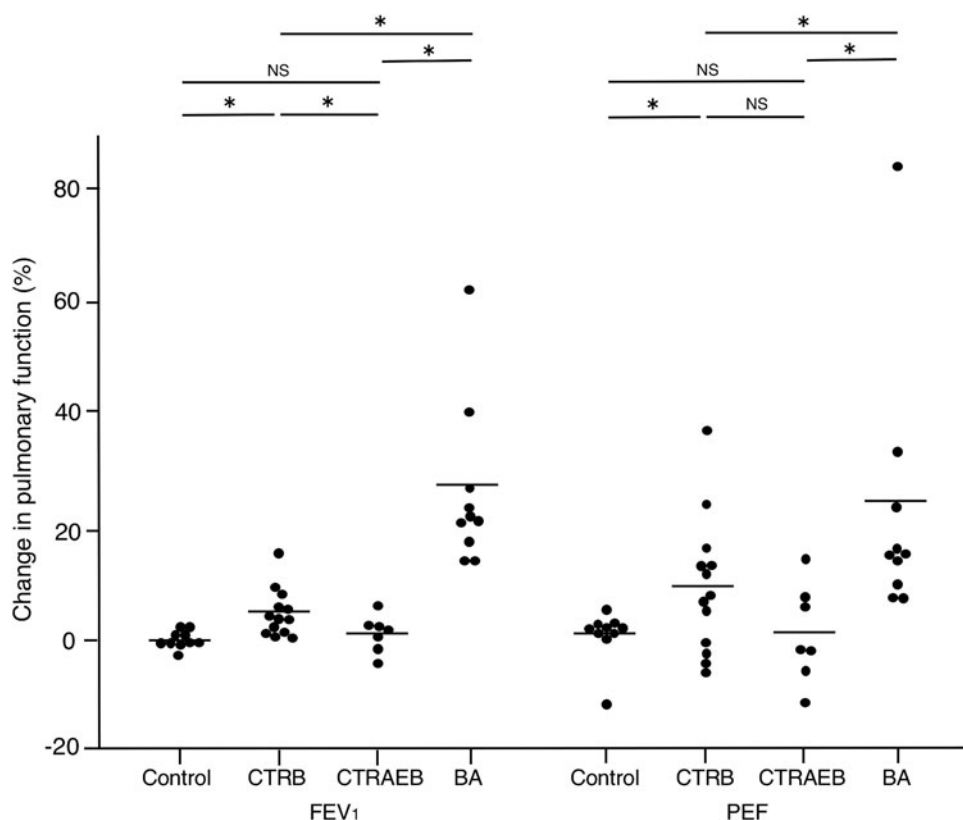


Figure 2. Changes in the FEV₁ and PEF rate observed on pulmonary function tests before and after inhalation of a SABA (0.03 mg procaterol hydrochloride) at the first examination of control subjects ($n = 10$), patients with CTRB ($n = 13$), patients with CTAEAB ($n = 7$), and patients with classic BA ($n = 10$). NS = not statistically significant. * $p < 0.05$ using Student's *t*-test.

and exhibited a negative response to inhalation of a β_2 -agonist. With inhalation of a SABA, the FEV₁ increased by 34 ± 117 mL ($1.3\% \pm 3.5\%$), and the PEF improved by 53 ± 530 mL/s ($1.3\% \pm 8.7\%$) (Figure 2).

Among the 13 patients with CTRB, 11 experienced chest tightness at the first examination and exhibited a positive response to inhalation of a β_2 -agonist. Two patients did not experience chest tightness at the first examination. With inhalation of a SABA, the FEV₁ increased by 128 ± 84 mL ($5.1\% \pm 4.0\%$) and the PEF improved by 545 ± 660 mL/s ($9.4\% \pm 11.7\%$).

Among the 10 patients with BA, all patients experienced dyspnea, cough, or wheezing at the first examination and exhibited a positive response to inhalation of a β_2 -agonist. With inhalation of a SABA, the FEV₁ increased by 436 ± 220 mL ($26.8\% \pm 14.3\%$) and the PEF improved by 764 ± 307 mL/s ($24.0\% \pm 22.2\%$).

Among the healthy subjects, all subjects experienced no respiratory symptoms and exhibited no response to inhalation of a β_2 -agonist. With inhalation of a SABA, the FEV₁ increased by -43 ± 38 mL ($-1.0\% \pm 1.0\%$) and the PEF improved by -64 ± 535 mL/s ($0.0\% \pm 5.6\%$).

Significant increases in FEV₁ were detected in patients with CTRB ($p = 0.0001$) and patients with BA

($p = 0.0002$) compared with that in control subjects. However, no significant differences were observed between patients with CTAEAB and control subjects ($p = 0.1273$). Significant differences were observed between patients with CTAEAB and patients with CTRB ($p = 0.0449$).

Significant increases in PEF were detected in patients with CTRB compared with that in control subjects ($p = 0.0326$). However, no significant differences were observed between patients with CTAEAB and control subjects ($p = 0.7500$) or between patients with CTAEAB and patients with CTRB ($p = 0.0982$).

Bronchial reactivity

Among the seven patients with CTAEAB, the bronchial responsiveness to methacholine was increased in two and not increased in four (Figure 3). One patient stopped the treatment because of severe chest tightness after inhalation of the methacholine solutions without exhibiting a 20% decrease in the FEV₁ relative to the post-saline control value.

Among the 13 patients with CTRB, the bronchial responsiveness to methacholine was increased in three and was not increased in eight. Two patients stopped

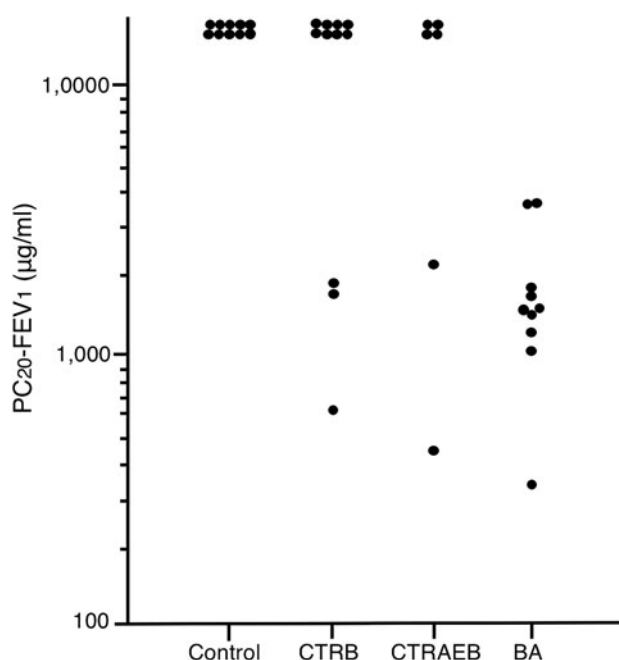


Figure 3. The provocative concentration of methacholine that produced a 20% decrease in the FEV₁ (PC₂₀-FEV₁) of control subjects ($n=10$), patients with CTRB ($n=11$), patients with CTRAEB ($n=6$), and patients with classic BA ($n=10$). Two patients with CTRB and one patient with CTRAEB stopped the treatment because they experienced severe chest tightness after inhalation of the methacholine solutions without exhibiting a 20% decrease in the FEV₁ relative to the post-saline control value.

the treatment because they experienced severe chest tightness after inhalation of the methacholine solutions without exhibiting a 20% decrease in the FEV₁ relative to the post-saline control value.

The bronchial responsiveness to methacholine was increased in all of the patients with BA. However, bronchial responsiveness to methacholine was not increased in the 10 healthy subjects.

Bronchial biopsies

Seven central biopsy specimens and seven peripheral biopsy specimens were obtained from patients with CTRAEB. No significant differences in cell numbers were detected between the two airway levels studied. We used the average cell numbers at the two airway levels in statistical analyses.

In all, 13 central biopsy specimens and 10 peripheral biopsy specimens were obtained from patients with CTRB. A central biopsy specimen was collected from only three patients. No significant differences in cell numbers were detected between the two airway levels studied. We used the average cell numbers at the two airway levels in statistical analyses.

In all, 11 central biopsy specimens and 11 peripheral biopsy specimens were obtained from the control subjects. No significant differences in cell numbers were observed between the two airway levels studied. We used the average cell numbers at the two airway levels in statistical analyses.

The numbers of cells in the biopsy specimens from the patients with chest tightness and the control subjects are presented in Figures 4 and 5. Significant increases in the numbers of CD3- ($p=0.0066$), CD4- ($p=0.0462$), CD8-positive cells ($p=0.0037$), and neutrophils ($p=0.0255$) were detected between patients with CTRAEB and control subjects. Significant increases in the numbers of mast cells ($p=0.0488$), CD3- ($p=0.0006$), CD4- ($p=0.0008$), CD8-positive cells ($p=0.0175$), neutrophils ($p=0.0275$), and macrophages ($p=0.0107$) were detected between patients with CTRB and control subjects. However, no significant differences in the number of eosinophils ($p=0.8360$) or mast cells ($p=0.6500$) were observed between patients with CTRAEB and control subjects, and no significant differences in the number of eosinophils ($p=0.2260$) were observed between patients with CTRB and control subjects.

Eosinophils in bronchial lavages and sputum samples

Seven BLF samples were obtained from patients with CTRAEB, 12 were collected from patients with CTRB, and 11 were collected from control subjects. We failed to obtain two BLF samples from one patient with CTRAEB and one patient with CTRB. An increased percentage of eosinophils in the BLF (5% or more) was detected in two patients with CTRB but not in patients with CTRAEB and control subjects (Figure 6). No significant differences between patients with CTRAEB and control subjects ($p=0.0816$) or between patients with CTRB and control subjects were observed ($p=0.0926$).

Seven sputum samples were obtained from patients with CTRAEB, 8 were collected from patients with CTRB, 10 were collected from patients with BA, and 11 were collected from control subjects (Figure 6). We failed to obtain sputum samples from four patients with CTRB and two control subjects. An increased percentage of eosinophils in the sputum (3% or more) was detected in two patients with CTRAEB and seven patients with BA but not in patients with CTRB and control subjects. No significant differences between the patients with CTRAEB and the control subjects ($p=0.0525$) and between the patients with CTRB and

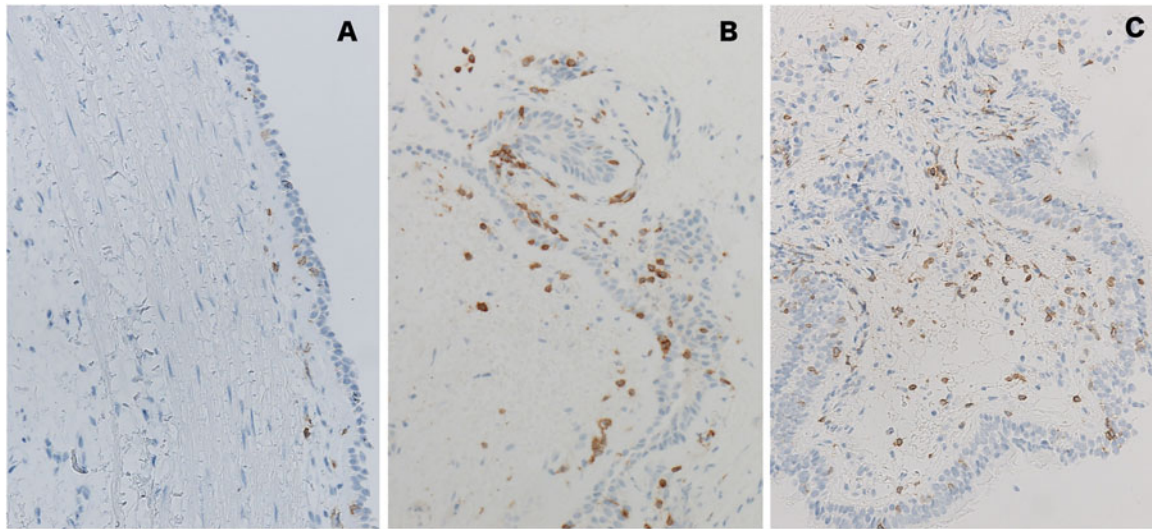


Figure 4. Typical bronchial biopsy specimens from a control subject (A), a patient with CTRB (B), and a patient with CTRAEB (C) stained with anti-CD3 antibody. The specimen from the patient with chest tightness contained many CD3-positive cells.

the control subjects ($p = 0.4090$) were observed. A significant difference between the patients with CTRAEB and the patients with CTRB ($p = 0.0211$) was detected.

Treatment

The responses of the patients with chest tightness to the asthma drugs are shown in Table 2. The effect of LTRA alone was inadequate in two patients with CTRAEB. We added ICS or TXSI, but these drugs had no effect. The patients' symptoms improved with a double dose prescription of LTRA.

Discussion

Retrosternal tightness or heavy sensation in the chest has been previously described as a typical symptom of patients with CTRB and tightness radiating to one side of the head, back, or chest [1,2]. A subset of these patients had chest tightness at sites other than the retrosternal area. This symptom is sometimes associated with coughing and sputum production. Patients with chest tightness have normal breath sounds, and the severity may vary from mild symptoms of light chest tightness that appear with a common cold to severe symptoms for which an ambulance is called. The frequency, duration, and onset time of chest tightness can also vary among different patients. These patients do not always have peripheral blood eosinophilia, an increase in the serum-nonspecific IgE level, or specific IgE positivity. In this study, very similar clinical characteristics were observed in patients with CTRAEB without BA.

In our previous report, patients with CTRB had significantly increased T-cell infiltration in the bronchial mucosal biopsy sample than controls; it was hypothesized that chest tightness arose from airway constriction due to T-cell inflammation [2]. In patients with CTRAEB without BA, whom we investigated in this study, we hypothesized that the chest tightness arose from inflammation alone, with a focus on airway T cells because there was significantly increased T-cell infiltration on bronchial mucosal biopsy, and symptoms did not improve with inhalation of bronchodilators. Because CTRB and CTRAEB present with highly similar clinical features, it is thought that they arise from excitation of the same neurological pathway [1]. The relationship between an onset of both clinical conditions and bronchial responsiveness to methacholine is currently unclear. In this study, there was little to distinguish CTRAEB from CTRB outside of the response to the bronchodilator.

The most characteristic feature of classic BA is bronchial inflammation leading to nonspecific hyper-reactivity. There are several reports of increased inflammatory cells in the airway mucosa of asthmatic patients [15–22]. Influx of eosinophils into the airway mucosa may be a characteristic of BA, which contrasts the low number of eosinophils in the airway mucosa of patients with CTRB and CTRAEB. In the GINA guidelines, chest tightness is listed as a symptom of asthma [10]. In our experience, asthma patients have the potential to experience CTRB and/or CTRAEB [1]. However, chest tightness has not been noted in most patients with BA. Based on our experience and other reports, CTRB and CTRAEB are often observed

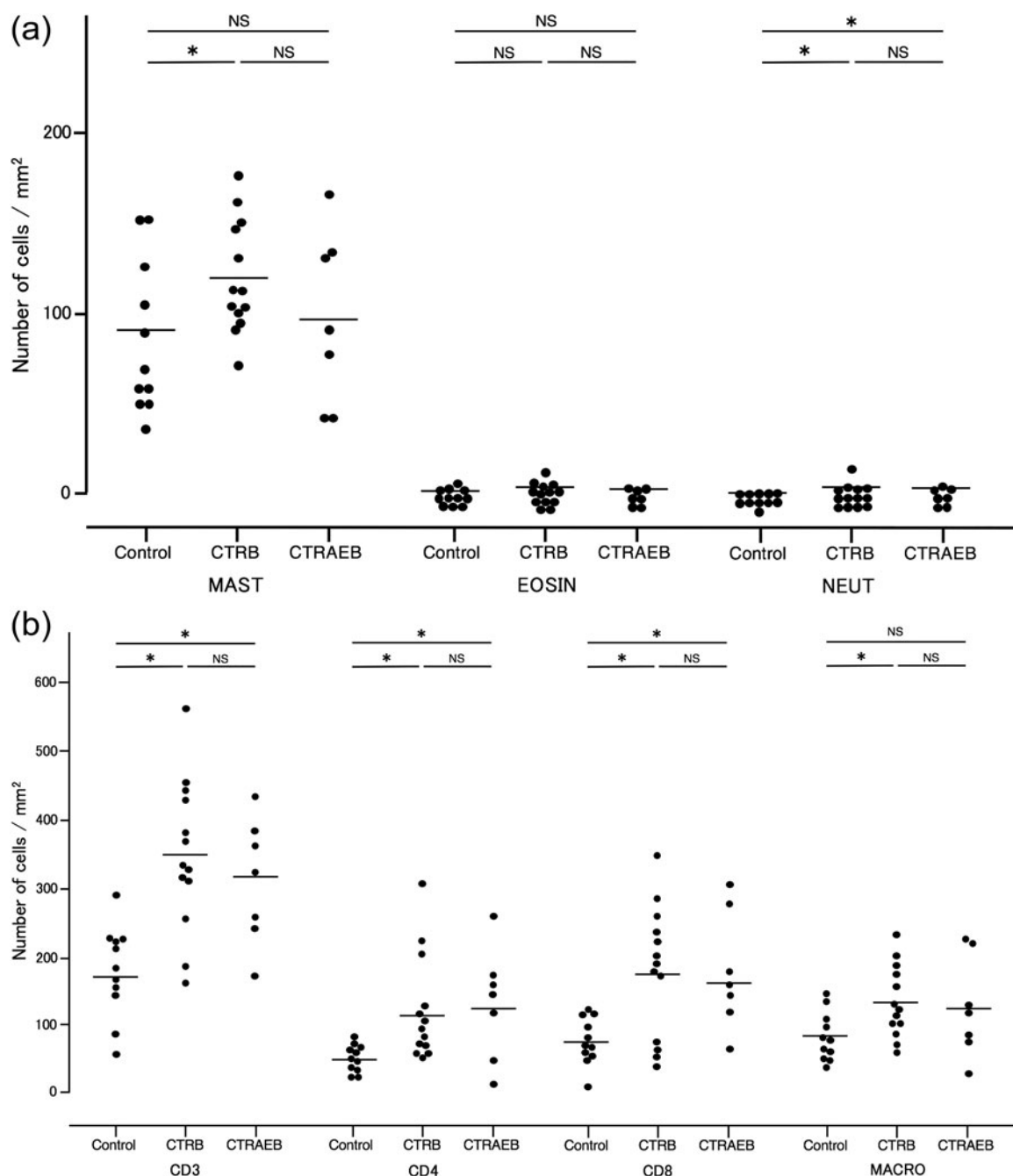


Figure 5. (a) The number of mast cells (MAST), eosinophils (EOSIN), neutrophils (NEUT), (b) CD3-, CD4-, and CD8-positive cells, and macrophages (MACRO) in the bronchial biopsy specimens of control subjects ($n=11$), patients with CTRB ($n=13$), and patients with CTRAEB ($n=7$) is presented per square millimeter. NS=not statistically significant. $*p < 0.05$ using the Mann-Whitney U-test.

as comorbidities in patients without BA, as in the present patient cohort, as well as in patients with other lung diseases, such as bronchiectasis, chronic lung infections, sarcoidosis, chronic obstructive pulmonary disease, lung cancer, and interstitial lung disease. Because bronchodilators are effective, clinical conditions presenting as CTRB without BA are thought to be a subtype of asthma and are called CPVA [1,3]. In previous reports, we suggested that CTRB may be

indicative of a variant form of asthma [2]. However, based on results from bronchial biopsy or airway hyperreactivity testing, only a fraction of patients with CTRB are thought to have characteristics that are vaguely similar to asthma while others appear to have low similarity to asthma. CTRAEB also differs from asthma in its characteristics and is thought to be a disease state arising from various pathological conditions. In our experience, CTRB and CTRAEB

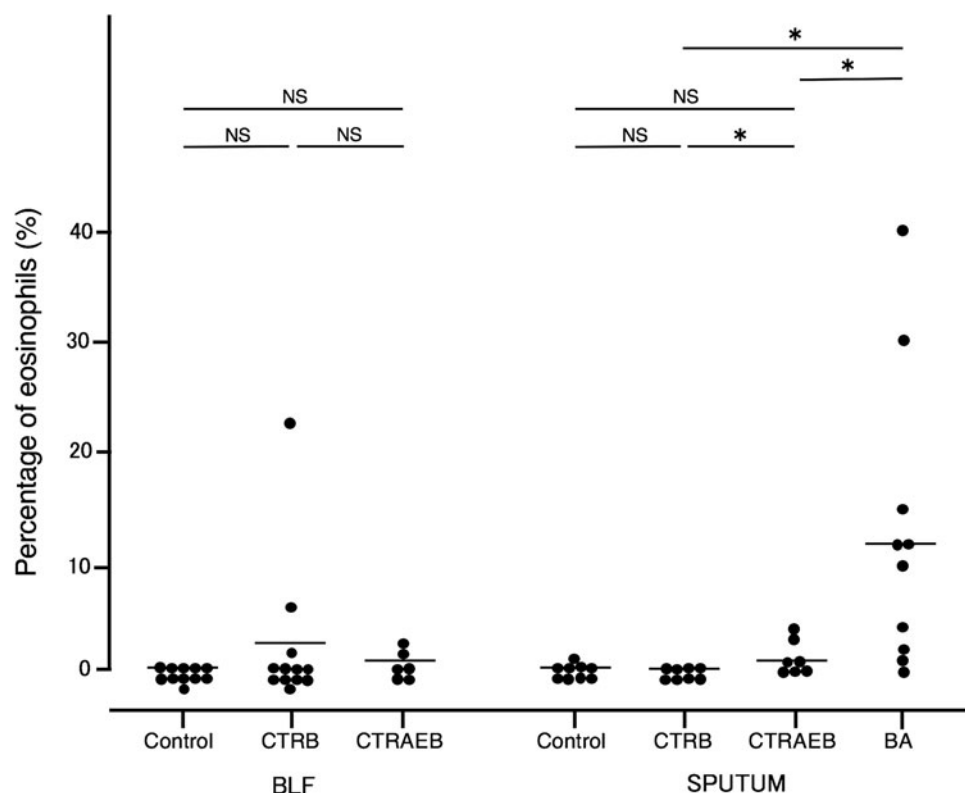


Figure 6. Percentages of eosinophils in BLF from control subjects ($n = 11$), patients with CTRB ($n = 12$), and patients with CTAEAB ($n = 6$). The percentages of eosinophils in the sputum from control subjects ($n = 9$), patients with CTRB ($n = 8$), patients with CTAEAB ($n = 7$), and patients with classic BA ($n = 10$). NS = not statistically significant. $*p < 0.05$ using the Mann–Whitney U-test.

Table 2. The responsiveness to asthma drugs among patients with chest tightness relieved with the use of asthma drugs except bronchodilators without BA.

Patient no.	SABA	LTRA	TXSI	ICS	Final control drugs
1	N	E	–	–	LTRA
2	N	E	–	–	LTRA
3	N	E	–	N	LTRA
4	N	E	N	N	LTRA
5	N	E	–	–	LTRA
6	N	E	–	–	LTRA
7	N	E	–	–	LTRA

E: effective against chest tightness; N: not effective against chest tightness.

sometimes occur in patients with BA independent of asthma attack control [1]. Second, we suggest that CTRB and CTAEAB are strongly associated with BA but differ from BA. CTRB and CTAEAB, based on clinical data and results from the bronchial mucosal biopsy, are concepts that include multiple pathological conditions rather than a single disease state; in other words, CTRB and CTAEAB are thought to be syndromes.

Patients with CTRB experiences relief from asthma drugs except bronchodilators [1,2]. Because CTRB is thought to arise from bronchial inflammation, it is thought that inhaled corticosteroid (ICS) treatments

similar to those for asthma would be useful. However, ICS treatments are not effective for everyone, and there are patients for whom an LTRA is more effective for alleviating symptoms [1,2]. CTAEAB is also thought to involve bronchial inflammation and might therefore respond adequately to ICS treatment, but for many patients, ICS treatments tend to be not very effective. Drugs such as LTRAs appear to be more effective. Because most patients with CTAEAB and CTRB respond to an LTRA in chest tightness, we speculated that these chest tightness may have been induced by the mechanisms involving leukotrienes. In our experience, a subset of CTAEAB patients recovered fully with treatment for several weeks. Additionally, at this stage, we cannot rule out the possibility that CTRB and CTAEAB are pathological conditions involving abnormalities in regions other than the respiratory tract.

We plan to design further studies to investigate these two clinical conditions referred to collectively as chest tightness relieved with asthma drug use (CTRA).

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