CASE REPORT

A case of atopic cough with aphonia showed a prominent response to a histamine H_1 receptor antagonist.

Masaki Hanibuchi[1, 4], Atsushi Mitsuhashi[2], Atsuro Saijo[1], Tatsuya Kajimoto[1], Seidai Sato[2], Tetsuya Kitagawa[3], and Yasuhiko Nishioka[2]

[1]Department of Respiratory Medicine, [3]Department of Cardiovascular Surgery, Shikoku Central Hospital of the Mutual aid Association of Public School teachers, Shikoku-Chuo, Japan, [2]Department of Respiratory Medicine and Rheumatology, [4]Department of Community Medicine for Respirology, Hematology and Metabolism, Graduate School of Biomedical Sciences, Tokushima University, Tokushima, Japan.

Abstract : A 33-year-old woman admitted to our hospital for further examination of severe non-productive cough lasting for about two months. Her symptom did not ameliorate by treatments including long acting β_2 agonists. She had a medical history of drug allergy to non-steroidal anti-inflammatory drugs. At the initial visit, she could not speak at all and communicated with us in writing. Chest auscultation revealed no wheezes, rhonchi and other crackles. Laboratory findings showed a mild eosinophilia with normal total and specific serum immunoglobulin E. The results of an electrocardiogram, a chest X-ray and a chest CT were unremarkable. A fractional exhaled nitric oxide value was within normal limit. Based on these observations, a diagnosis of atopic cough (AC) was suspected, and we started treatment with a histamine H_1 receptor antagonist (H_1-RA). She had become able to speak again in association with complete disappearance of cough by eight-weeks after treatment initiation, and her symptoms did not recur even after cessation of treatment. By the confirmation of remarkable clinical improvement in response to a H_1-RA, a diagnosis of AC was made. To the best of our knowledge, this is the first report of an AC patient who presented severe cough with aphonia. J. Med. Invest. 70 : 281-284, February, 2023

Keywords **:** *atopic cough, aphonia, bronchodilator resistant chronic cough, histamine H_1 receptor antagonist*

INTRODUCTION

Chronic cough is one of the most common symptoms for which patients seeking medical attention in general practice (1). In Japan, cough variant asthma (CVA) is the most common etiology of chronic cough, followed by post-infectious cough, atopic cough (AC), gastroesophageal reflux disease, and sinobronchial syndrome (2, 3). AC has been proposed as one of the major causes of persistent cough in 1992 (4), and defined as a chronic bronchodilator resistant non-productive cough with global atopic tendency, eosinophilic tracheobronchitis with no variable airflow obstruction, and increased cough reflex sensitivity without nonspecific bronchial hyperresponsiveness (5). Persistent non-productive cough with "tickle" in the throat is the only symptom of AC in most cases (6), and there are no case series of AC patients with comorbid aphonia.

In the present report, we demonstrated a rare case of AC who complained persistent non-productive cough with aphonia, and highlighted the significant therapeutic efficacy of a histamine H_1 receptor antagonist (H_1-RA).

CASE REPORT

A 33-year-old woman admitted to our hospital for further examination of severe non-productive cough lasting for about two months. Her symptom did not ameliorate by long acting β_2 agonists, clarithromycin, proton pump inhibitors and antitussive agents prescribed in a nearby clinic. She had a medical history of drug allergy to non-steroidal anti-inflammatory drugs. Although no past histories of other allergic diseases, such as asthma and CVA, were reported, she sporadically experienced non-productive cough provoked by cold air exposure, passive smoking and conversation for about 20 years. She was a lifetime non-smoker, and no significant social and family histories were reported. She was an office worker and lived in a 10-year-old reinforced concrete house.

At the initial visit, she could not speak at all and communicated with us in writing by using her mobile phone. She also complained of ticklish throat discomfort and sore throat. The physical examinations at the initial admission revealed body temperature of 36.1 ℃, blood pressure of 120/68 mmHg, pulse of 70 beats per minute and percutaneous oxygen saturation of 98% on room air. Throat was slightly injected, but tonsils were not swollen. Cardiac examination was entirely within normal limits. Chest auscultation revealed no wheezes, rhonchi or other adventitious lung sounds even in forced expiration. No evident pretibial and foot pad edema were seen. The remainder of physical examinations was also normal. Hematological findings showed normal white blood cell count (7,200 /μL) with mild eosinophilia (180 /μL). C-reactive protein was 0.05 mg/dL and the total serum immunoglobulin E (IgE) level was 29.6 U/mL. Specific IgE antibody was negative against mold mix, *Dermatophagoides pteronyssinus* (Der p), house dust 1, dog dandruff, ragweed,

Abbreviations :
CVA, cough variant asthma ; AC, atopic cough ; H_1-RA, histamine H_1 receptor antagonist ; IgE, immunoglobulin E ; Der p, *Dermatophagoides pteronyssinus* ; FeNO, fractional exhaled nitric oxide : ppb, parts per billion ; VAS, visual analogue scale ; ICS, inhaled corticosteroid ; FACC, fungus-associated chronic cough

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Address correspondence and reprint requests to Masaki Hanibuchi, Department of Community Medicine for Respirology, Hematology and Metabolism, Graduate School of Biomedical Sciences, Tokushima University, 3-18-15 Kuramoto-cho, Tokushima 770-8503, Japan and Fax : +81-88-633-2134. E-mail : +halhoney@tokushima-u.ac.jp

mugworth, cedar, cocksfoot and cypress. The remainder of laboratory test results is shown in Table 1. Both an anti-mycoplasma antibody and anti-pertussis toxin antibodies, which were measured in a nearby clinic, were negative. The results of an electrocardiogram, a chest X-ray and a chest CT were unremarkable. A value of fractional exhaled nitric oxide (FeNO) was within normal limit at 7 parts per billion (ppb). A pulmonary function test was not performed following the patient's wishes. Otorhinolaryngological examinations including the nose, pharynx, larynx, and vocal cord were nothing in particular. Moreover, neurologic and psychiatric investigations revealed no significant abnormalities.

Based on these observations, a diagnosis of AC was suspected, and we started treatment with a H_1-RA, bilastine 20 mg/day, at the initial visit. At two-weeks after treatment initiation, her symptom markedly improved, and she had become able to speak again in association with complete disappearance of severe cough by eight-weeks after treatment initiation. In addition, her symptoms did not recur even after cessation of treatment. By the confirmation of remarkable clinical improvement in response to a H_1-RA, a diagnosis of AC was made.

In this case, we evaluated degrees of her symptoms by the visual analogue scale (VAS) score. The patient was instructed to check present degree of symptoms in the VAS score sheet at every visit. The VAS scores of symptoms were defined as follows : a degree of symptom at the initial visit was 10 points and symptom-free state was 0 point. As shown in Figure 1, the VAS scores of symptoms remarkably improved by the treatment with a H_1-RA.

DISCUSSION

Chronic cough is a common and distressing symptom in general practice (1), however proper diagnosis of its etiology is often difficult (7). As persistent cough is well known to be associated with marked deterioration in quality of life in some patients (8), the appropriate diagnosis of the etiology is an important clinical concern for the adequate treatment and symptom relief of suffering patients.

A definite diagnosis of AC is made when following all criteria of the Japanese Cough Research Society (9) were satisfied : 1) presence of chronic non-productive cough, 2) atopic constitution and/or induced sputum eosinophilia, 3) no bronchial reversibility, 4) normal bronchial responsiveness, 5) increased cough reflex sensitivity, 6) resistance to bronchodilators, 7) normal chest X-ray, and 8) normal lung function. However, the tests required for diagnosing AC, such as cough reflex sensitivity test for capsaicin, bronchial challenge test and induced sputum analysis, are technically demanding and require specialized instruments and personnel (10, 11). Therefore, their use is restricted to specialist

Table 1. Laboratory data at the initial visit

Hematology					
WBC	7,200	/μL	BUN	11.8	mg/dL
Neu	65.7	%	Cre	0.69	mg/dL
Lymph	23.2	%	UA	4.5	mg/dL
Mono	8.5	%	Na	143	mEq/L
Eos	2.5	%	K	4.2	mEq/L
Baso	0.1	%	Cl	107	mEq/L
RBC	472×10^4	/μL	CRP	0.05	mg/dL
Hb	14.4	g/dL	BS	85	mg/dL
Ht	42.5	%			
Plt	20.5×10^4	/μL	Allergic test		
			Total IgE	29.6	U/mL
Biochemistry			Specific IgE		
AST	17	IU/L	Mold mix	0.04	IU/mL
ALT	17	IU/L	Der p	0.03	IU/mL
ALP	50	U/L	House dust 1	0.02	IU/mL
LDH	166	IU/L	Dog dandruff	<0.01	IU/mL
γ-GTP	11	U/L	Ragweed	<0.01	IU/mL
CK	81	U/L	Mugworth	0.02	IU/mL
T-bil	1.2	mg/dL	Cedar	<0.01	IU/mL
TP	7.2	g/dL	Cocksfoot	<0.01	IU/mL
Alb	4.7	g/dL	Cypress	<0.01	IU/mL
T-cho	179	mg/dL			
TG	58	mg/dL	Pulmonary function test		
HDL-cho	73	mg/dL	FeNO	7	ppb
LDL-cho	88	mg/dL			
Amy	137	IU/L			

IgE, immunoglobulin E ; Der p, *Dermatophagoides pteronyssinus* ; FeNO, fractional exhaled nitric oxide ; ppb, parts per billion

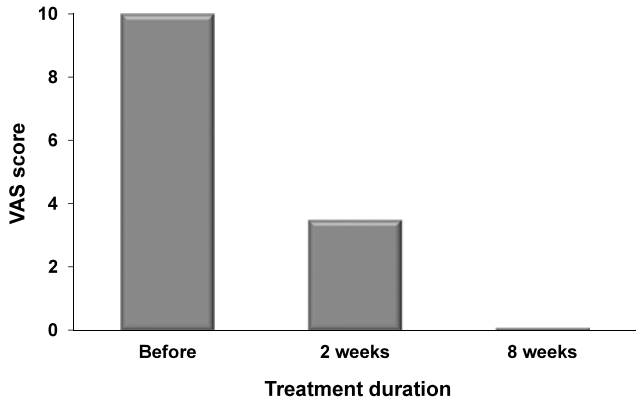

Figure 1. Comparison of the VAS scores of symptoms before and after treatment for AC. The VAS scores remarkably decreased at two and eight weeks after treatment initiation compared with that at the initial admission.

centers. In case of above-mentioned criteria are not satisfied, an alternative diagnostic criterion has also been proposed and we are able to make a diagnosis of AC when all of the following were present : 1) non-productive cough without wheezing or dyspnea ; 2) cough resistant to bronchodilator therapy ; 3) presence of findings indicative of atopic disposition ; and 4) complete relief of cough after treatment with H_1-RAs and/or glucocorticoids (9). As the patient fulfilled an "alternative diagnostic criterion", we made a diagnosis of AC in this case. The complete relief of her symptoms within two months of treatment reinforced a diagnosis of AC, because it was an important factor in making a diagnosis (9).

The typical symptom of AC is chronic non-productive cough with a sensation of irritation in the throat, and that is the sole complaint in most cases. For example, Ogawa *et al*. reported four patients of AC who had persistent non-productive cough with ticklish throat discomfort, which was their only symptom (12, 13). To the best of our knowledge, this is the first report of an AC patient who presented severe non-productive cough with comorbid aphonia. As shown in Table 2, structural and functional abnormalities in the larynx and vocal cord as well as neurogenic and psychogenic disorders are considered to be the causes of aphonia (14). However, otorhinolaryngologic, neurologic and psychiatric examinations revealed no significant abnormalities in this case. In addition, the patient had become able to speak again in association with complete disappearance of cough after treatment, while she could not speak at all at the initial visit. Taken together, it was considered reasonable that severe cough was associated with the cause of aphonia in this patient, whereas the pathogenic mechanisms of aphonia remained to be elucidated. There are few reports regarding the relationship between respiratory diseases and aphonia. Orlando *et al*. showed a case developed an upper airway syndrome ensued with aphonia as well as non-specific bronchial hyperreactivity, obstructive bronchiolitis after exposure to hydrobromic acid fumes (15). Bhalla *et al*. prospectively assessed the impact of inhaled corticosteroid (ICS) on the larynx and pharynx in asthmatic patients. Regular ICS users had significantly more pharyngeal inflammation and were more likely to have hoarseness, weakness of voice, aphonia, sore throat, throat irritation, and cough (16). Although the present case did not have histories of exposure to harmful fumes and ICS use, undetectable edema and inflammation in the larynx and pharynx might be involved in the pathogenesis of aphonia. Further studies are warranted to clarify the causes of aphonia in patients with AC.

Chronic cough in patients with AC characteristically responds to H_1-RAs and/or glucocorticoids, but not to bronchodilators (17). Shioya *et al*. conducted a prospective study to evaluate antitussive effects of a H_1-RA, epinastine, in AC patients and demonstrated that treatment with epinastine significantly improved the cough scores and the cough threshold for capsaicin (6). In the present case, treatment with a H_1-RA also revealed a drastic therapeutic effect on severe cough with comorbid aphonia. Increased cough reflex sensitivity is one of the major physiological features of AC and cough hypersensitivity was reported to be induced by chemical mediators, such as histamine (18). Thus, H_1-RAs could inhibit detrimental functions of histamine, which led to improve cough threshold and reduce cough hypersensitivity. Although the optimal dose and treatment duration for reducing cough remains unclear, these observations strongly indicated the usefulness of H_1-RAs for treating AC patients suffering from persistent cough.

In an animal model mimics some characteristics of AC, sensitization with the protein fraction of a fungus enhanced the irritability of cough receptors to tussive stimuli (19). Moreover, previous clinical evidence suggested that hypersensitivity to several fungal antigens could induce AC (12, 13). Recently, fungus-associated chronic cough (FACC) was introduced as a new chronic cough condition. FACC is defined as chronic cough associated with fungi, and recognition of FACC has provided the possibility to use antifungal drugs for severe chronic cough as new treatment strategies (20). Therefore, the identification of causative antigens is strongly recommended through environmental surveys and fungal culture of sputum and pharyngeal swabs, especially in patients with severe chronic cough. It might be the major disadvantage that we could not sufficiently carry out examinations of causative antigens of the disease including fungi in the present case.

In conclusion, we herein reported a rare case of AC who had severe chronic cough with comorbid aphonia. A drastic improvement of symptom in response to treatment with a H_1-RA led to a diagnosis of AC. Otorhinolaryngologic, neurologic and

Table 2. The causes of aphonia

Structural organic disorder	
	Laryngeal edema (inflammation, allergy)
	Vocal cord nodule (polyp, cyst, papilloma)
	Presbylarynx
Neurogenic organic disorder	
	Vocal tremor
	Spasmodic dysphonia
	Vocal cord paralysis
Functional disorder	
	Vocal fatigue
	Muscle tension aphonia
	Ventricular phonation
Psychogenic disorder	
	Psychogenic aphonia
	Hysterical aphonia

psychiatric examinations revealed no significant abnormalities, suggesting that severe cough was associated with the cause of aphonia in the present patient. To the best of our knowledge, this is the first report of an AC patient who presented severe cough with aphonia.

CONFLICT OF INTEREST DISCLOSURE

All authors declare no conflicts of interest associated with this work.

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