

Dear Editor

It is Time to Call Attention to the Clinical Significance of Fungal Colonization in Chronic Cough

Central sensitization, including abnormal laryngeal paresthesia, is recognized as a potential mechanism underlying chronic cough.¹ Our recent study showed that among the various types of laryngeal paresthesia,^{2,4} a peculiar laryngeal sensation presenting as a sensation of mucus in the throat (SMIT) is correlated with fungal colonization in chronic cough patients.⁵ The presence of basidiomycetous (BM) fungi in induced sputum has been reported to be an important clinical finding associated with chronic idiopathic cough (CIC). Further studies demonstrated that low-dose itraconazole (ITCZ) therapy did not provide sufficient relief of cough symptoms itself in CIC patients; however, SMIT was successfully treated with the therapy.⁶

Fungus-associated chronic cough (FACC) is a recently introduced clinical concept encompassing a number of chronic cough conditions⁷ including the following manifestations: (i) chronic cough; (ii) the presence of environmental fungi in sputum, particularly BM fungi,⁸ which are well known to act as airborne allergens⁸; and (iii) a good clinical response to antifungal drugs. Therefore, in FACC patients, SMIT may be treated sufficiently together with cough itself with antifungal drugs.

To clarify the clinical significance of fungal colonization in chronic cough patients, we report the results of a preliminary study regarding the recent prevalence of chronic cough in Saiseikai Kanazawa Hospital, and the positive rates of both fungal colonization and SMIT in chronic cough patients. The medical records of 106 patients complaining of cough lasting 8 weeks or longer, who visited our clinic from

1 April to 31 December 2012, were collected and reviewed retrospectively. The patients had a median age of 51.0 (range: 19-82) years, and 60.7% were female. The causes of chronic cough were diagnosed based on the diagnostic criteria of causes of chronic cough recommended by the Japanese Cough Research Society,⁹ and the American College of Chest Physicians evidence-based practice guidelines. Definite FACC was diagnosed with the strict exclusion of other causes of chronic cough. Unexplained chronic cough (UCC) remained after diagnosis of sinobronchial syndrome (SBS), cough variant asthma (CVA), atopic cough (AC), or gastroesophageal reflux (GER)-associated cough. These UCC patients included a cluster of chronic cough patients whose sputum culture yielded BM fungi and in whom antifungal drugs showed sufficient efficacy. Such patients were diagnosed as FACC and then excluded from UCC.

Among the 106 patients who were adequately assessed, a diagnosis was made in 93 patients (87.7%): AC in 29 (27.4%); CVA in 22 (20.8%); SBS in 21 (19.8%); FACC in 13 (12.3%); GER-associated cough in 4 (3.8%); psychogenic cough in 4 (3.8%); and UCC in 13 (12.3%) (Table 1). Fungal culture of the sputum was obtained from 101 patients and the profiles were as follows: *Aspergillus fumigatus*, 23 patients; BM fungi, 20 patients; *Aspergillus niger*, 17 patients; *Candida albicans*, 11 patients; *Penicillium* spp., 2 patients; and *Aspergillus flavus*, 2 patients. BM fungi were the 2nd most common type of fungi after *A. fumigatus*. These environmental fungi were detected from patients with cough of various causes in various degrees.

Although we seldom experience the necessity for eradicating *Candida* or *Penicillium* spp. from the sputum of chronic cough patients, further research is needed to determine whether *A. fumigatus*, which is known to be associated with sensitization of asthma or progression of ABPA, or *A. niger*, which has been reported to be one of causative antigens of eosino-

Table 1 The ratio of positive results of fungal colonization in sputum and presence of SMIT

	AC	CVA	SBS	FACC	GER	Psy	UCC
Number of patients	29	22	21	13	4	4	13
Positive results of fungal cultures (%)							
<i>Aspergillus fumigatus</i>	4 (14)	4 (18)	5 (24)	3 (23)	0 (0)	0 (0)	7 (54)
<i>Basidiomycetous fungi</i>	1 (4)	3 (15)	3 (15)	13 (100)	0 (0)	0 (0)	0 (0)
<i>Candida</i>	4 (14)	2 (9)	2 (10)	0 (0)	2 (50)	0 (0)	1 (8)
<i>Aspergillus niger</i>	4 (14)	2 (9)	5 (24)	0 (0)	0 (0)	1 (25)	5 (38)
<i>Penicillium</i> spp.	0 (0)	1 (5)	0 (0)	0 (0)	0 (0)	0 (0)	1 (8)
<i>Aspergillus flavus</i>	1 (3)	0 (0)	1 (5)	0 (0)	0 (0)	0 (0)	0 (0)
Presence of SMIT	12 (41)	8 (36)	8 (38)	11 (85)	3 (75)	0 (0)	6 (46)

SMIT, a sensation of mucus in the throat; AC, atopic cough; CVA, cough variant asthma; SBS, sinobronchial syndrome; FACC, fungus-associated chronic cough; GER, gastroesophageal reflux-associated cough; Psy, psychogenic cough; UCC, unexplained chronic cough.

philic pneumonia, should also be eradicated. Therefore, we decided not to diagnose such patients as FACC but as UCC at present.

Similar to the other detected environmental fungi, BM fungi are widely distributed around the world, it is reasonable that they were detected from the sputum samples obtained from various cough patients. However, it is necessary to investigate whether additional therapies for FACC would also be efficacious against SMIT, which is represented as a cough-related laryngeal sensation of the patients with chronic cough other than FACC.

In this study, there were no significant correlations between the presence of SMIT and presence of specific fungi (*A. fumigatus* N.S. and BM fungi $P = 0.08$); however, there were significant correlations between SMIT and the presence of *A. fumigatus* or BM fungi ($P < 0.05$). Therefore SMIT may predict colonization by fungi, including BM fungi, in chronic cough patients. It is surprising that the positive ratio of BM colonization in chronic cough patients was relatively high, and that FACC was the fourth major cause of chronic cough in this study.

In chronic cough patients suffering from SMIT, attempts to detect fungal colonization in bronchial specimens should be started at the beginning of the diagnostic process of chronic cough rather than waiting until after thorough systematic investigation for new management of cough and cough-related laryngeal sensations.

ACKNOWLEDGEMENTS

Authors' contributions: HO, NO and KM all belong to Fungus Association Cough Research Society in Japan. Statistical analysis was performed by NO. Especially KM contributed to identifying fungi. MF is general conductor of this study.

Haruhiko Ogawa¹, Masaki Fujimura², Noriyuki Ohkura³ and Koichi Makimura⁴

¹ Division of Pulmonary Medicine, Ishikawa-ken Saiseikai Kanazawa Hospital, ²Respiratory Medicine, National Hospital Organization Nanao Hospital, ³Respiratory Medicine, Ishikawa Prefectural Central Hospital, Ishikawa and ⁴Laboratory of Space and Environmental Medicine, Teikyo University, Tokyo, Japan
Email: saiseikh@po3.nsknet.or.jp

Conflict of interest: No potential conflict of interest was disclosed.

REFERENCES

1. Ryan NM, Birring SS, Gibson PG. Gabapentin for refractory chronic cough: a randomised, double-blind, placebo-controlled trial. *Lancet* 2012;**380**:1583-9.
2. Deary IJ, Wilson JA, Harris MB, MacDougall G. Globus pharyngis: development of a symptom assessment scale. *J Psychosom Res* 1995;**39**:203-13.
3. Vertigan AE, Gibson PG. Chronic refractory cough as a sensory neuropathy: evidence from a reinterpretation of cough triggers. *J Voice* 2011;**25**:596-601.
4. Matsumoto H, Tabuena RP, Niimi A *et al.* Cough triggers and their pathophysiology in patients with prolonged or chronic cough. *Allergol Int* 2012;**61**:123-32.
5. Ogawa H, Fujimura M, Takeuchi Y, Makimura K. Dealing with a sensation of mucus in the throat in chronic cough management. *Respirology* 2013;**18**:732-3.
6. Ogawa H, Fujimura M, Takeuchi Y, Makimura K. Clinical experience with low-dose itraconazole in chronic idiopathic cough. *Cough* 2013;**9**:1.
7. Birring SS. New concepts in the management of chronic cough. *Pulm Pharmacol Ther* 2011;**24**:334-8.
8. Helbling A, Brander KA, Horner WE, Lehrer SB. Allergy to basidiomycetes. *Chem Immunol* 2002;**81**:28-47.
9. Committee for the Japanese Respiratory Society Guidelines for Management of Cough, Kohno S, Ishida T *et al.* The Japanese Respiratory Society guidelines for management of cough. *Respirology* 2006;**11** (Suppl 4):S135-86.