

The Definitive Diagnostic Process and Successful Treatment for ABPM Caused by *Schizophyllum commune*: A Report of Two Cases

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ABSTRACT

Background: Although mucoid impaction of the bronchi (MIB) is a well-known manifestation in allergic bronchopulmonary mycosis (ABPM), when unknown samples or plural eumycetes are cultured from bronchial materials, several problems are encountered which can affect the definitive diagnostic process or successful treatment.

Case Summary: The definitive diagnostic process of two patients [a 58-(Case 1) and a 70-(Case 2) year-old female] with MIB was: 1) to identify the existence of any allergic respiratory disorder, 2) to detect the fungi obtained from bronchial materials, with use of the 28S rDNA sequencing and analysis, 3) to investigate whether the detected fungus was a probable etiologic antigen, and 4) to make the final diagnosis based on the results of the inhalation examinations using the antigenic solution of the fungi. As a treatment strategy, bronchial toilet and low dose itraconazole therapy were planned according to the clinical manifestations of each patient.

Discussion: The two patients with MIB were successfully diagnosed as ABPM caused by *Schizophyllum commune* (Sc-ABPM) accompanied with hyperattenuating mucoid impaction. The reliability of some allergological makers as a substitution for the bronchoprovocation test should be clarified in near future. Clinical manifestations demonstrated in our cases suggested that the allergic reaction such as eosinophilic bronchoalveolitis spreading around the mucus plug was a primary lesion underlying the Sc-ABPM. The success of the treatment for Sc-ABPM will be achieved by the strategy targeting to fundamental condition and by the control of the disease recurrence by means of effective environmental management.

KEY WORDS

allergic bronchopulmonary mycosis, hyperattenuating mucoid impaction, mucoid impaction of the bronchi, *Schizophyllum commune*, specific-IgE for *Schizophyllum commune*

ABBREVIATIONS

MIB, mucoid impaction of the bronchi; ABPM, allergic bronchopulmonary mycosis; ABPA, allergic bronchopulmonary aspergillosis; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second; BALF, bronchoalveolar lavage fluid; ITCZ, itraconazole.

INTRODUCTION

When allergic bronchopulmonary mycosis (ABPM)¹ is considered in a patient with mucoid impaction of

the bronchi (MIB),² the clinical diagnosis is often based on the diagnostic criteria for allergic bronchopulmonary aspergillosis (ABPA)³ as described by Rosenberg. It is true that the accuracy of molecular

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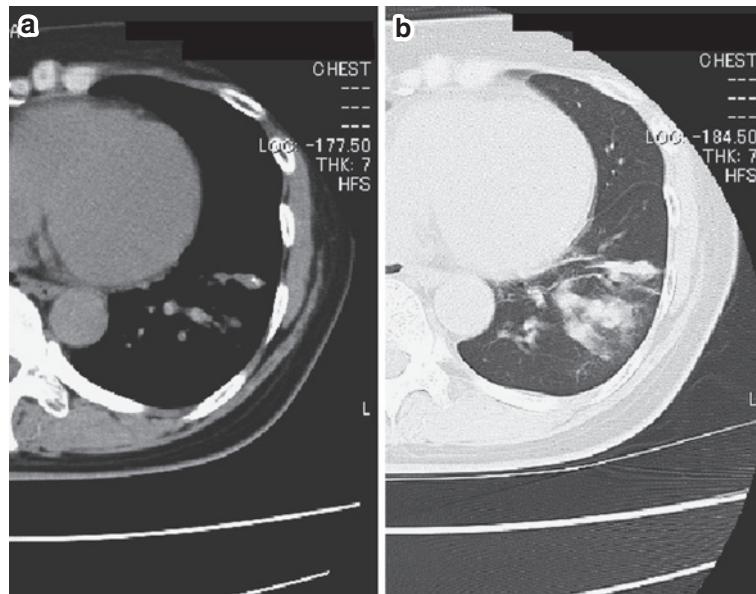


Fig. 1 **a:** Mediastinal window of computed tomography of the chest showing high attenuation bronchial mucous pluggings in the left B⁸ bronchus in Case 1. **b:** Computed tomography of the chest showing mucus plugs in the left B⁸⁻¹⁰ bronchi surrounded by small granular shadows in the left S⁹.

analyses for identifying environmental fungi has greatly improved in recent years, but when unknown samples or plural eumycetes are cultured from bronchial materials of MIB patients, meticulous attention to details will be necessary to diagnose ABPM according to the diagnostic criteria of ABPA.⁴

We have proposed a diagnostic process of allergic fungal respiratory disease⁵ consisting of the following 4 steps; 1) to try to identify the existence of any allergic respiratory disorder (eosinophilia in the sputum and/or BALF, tissue eosinophilia in the specimen of transbronchial lung biopsy), 2) to detect and identify the fungi obtained from bronchial materials (especially BALF or mucous plug [repeated samples of sputum are substituted when previous two materials are not available]), with use of the 28S rDNA (D1/D2) sequencing and analysis, 3) to investigate whether the detected fungus was a probable etiologic antigen; skin reaction and/or precipitating antibody and/or the fungus specific IgE, and 4) to make the final diagnosis based on the results of the inhalation examinations using the antigenic solution of the fungi.

This diagnostic process allowed us to overcome the difficulties and the problems associated with diagnosing ABPM based on the diagnostic criteria for ABPA, and the two patients with MIB were successfully diagnosed as ABPM caused by *Schizophyllum commune* (*S. commune*) (Sc-ABPM). Although the efficacy of antifungal therapy in some ABPA patients has already been reported,⁶ the therapeutic strategy for Sc-ABPM has not been still established. Based on

the clinical manifestations which were demonstrated in our present cases, we hypothesized the primary lesion responsible for Sc-ABPM, and subsequently adjunctive therapies such as bronchoscopic suctioning and flushing² or the itraconazole (ITCZ) therapy⁷ were planned. The recurrence of the disease experienced in our case of Sc-ABPM suggested both the importance of evaluating the existence of environmental fungi and the necessity for improved environmental management.

CLINICAL SUMMARY

CASE REPORT 1

A 58-year-old female patient was admitted to our hospital on January 4, 2007 for investigation of a productive cough and abnormal pulmonary infiltrates. Symptoms of cough and sputum developed in December 2006 and had not since improved. Physical examination revealed the following: her temperature was 36.2°C, and her heart rate 98 beats per minute. Auscultation did not reveal any abnormalities, such as wheezes or rhonchi.

Laboratory studies showed a white blood cell count of 4,900 per μ l with 20.9% eosinophils. No inflammatory reactions were observed as assessed by C-reactive protein level and erythrocyte sedimentation rate (ESR). Radioimmunosorbent tests revealed elevated total IgE levels in the serum (805 U/ml), and the results of radioallergosorbent test for specific IgE antibodies against *Aspergillus*, *Penicillium*, *Candida*, and *Alternaria* were 1.08, 2.49, 0.91, and 0.48 (U_A/mL), respectively. Differential cell analysis of sputum

Table 1 Characteristics of the two patients with ABPM caused by *Schizophyllum commune*

		Case 1	Rosenberg	Case 2	Rosenberg
Age		58		70	
Gender		F		F	
The existence of eosinophilic involvement	Sputum (%)	89		77	
	Mucus plug	Positive		Positive	
	TBBB	Positive		Positive	
The fungi obtained from bronchial materials	Sputum	<i>S. commune</i>	Yes	<i>B. adusta</i>	No
	Mucus plug			<i>S. commune</i> , <i>C. albicans</i>	
	BAL	<i>S. commune</i>			
Immediate skin reactivity to <i>S. commune</i>		9 × 9/27 × 29	Yes	16 × 20/48 × 60	Yes
Arthus reactivity (late skin reactivity) to <i>S. commune</i>		(-)	No	20 × 20/80 × 150	Yes
The fungus specific IgE (kIU/L)		1.34		3.37	
The fungus specific IgG (mgA/L)		10.7		2.84	
The bronchoprovocation test	Positive	<i>S. commune</i>		<i>S. commune</i>	
	Negative	<i>A. niger</i>		<i>B. adusta</i> , <i>Candida</i>	
Asthma		(-)	No	(-)	No
Peripheral blood eosinophilia (%)		20.9	Yes	9.4	Yes
Precipitating antibodies against <i>S. commune</i> antigen		(-)	No		
Elevated serum immunoglobulin E concentrations (IU/ml)		805	Yes	787	Yes
History of pulmonary infiltrates (transient or fixed)		MIB, HAM	Yes	HAM, Consolidation	Yes
Central bronchiectasis		(-)	No	(+)	Yes
History of expectoration of brown plugs or flecks		(-)	No	(+)	Yes
Fever		(-)		(+)	
Environmental provocation tests		(-)		(+)	
Relapse		(-)		(+)	
Survey of environmental fungi		Not particular		<i>S. commune</i>	
Forced vital capacity (FVC) (L)		2.84 (108.0%)		2.56 (113.3%)	
Forced expiratory volume in 1 second (FEV1) (L)		2.31 (100.0%)		1.90 L (113.8%)	
FEV1/FVC ratio		81.3%		74.2%	
PC20 (mg/ml)		>20		2.02	

revealed marked eosinophilia (4% alveolar macrophages, 7% neutrophils, and 89% eosinophils).

Chest radiographs taken upon admission showed consolidation on the left lung field. Mediastinal window of computed tomography of the chest showed high attenuation bronchial mucous plugs⁸ in the left B⁸ bronchus (Fig. 1a), and a corresponding section on the lung window demonstrated the mucus-filled dilated bronchi and extensive bronchiectasis (Fig. 1b).

Bronchoscopy revealed thick green mucous plugs in the left B^{9a} and B¹⁰. Histological examination of transbronchial bronchial biopsy specimens obtained from the bifurcation of the left B⁸ and the left B⁹ showed infiltration of eosinophils into the wall of the bronchial mucosa but no fungal spores or hyphae. By using 28S rDNA (D1/D2) sequencing and analyses, the basidiomycetous fungus obtained from the sputum samples and bronchial samples of this patient were both identified as *S. commune*.

The immediate (15 min) skin reaction was 9 × 9/27 × 29 for *S. commune*, and 10 × 8/36 × 28 for *Aspergillus niger* (*A. niger*); The results were judged to be

positive because of the longer axis of the flare beyond 9 mm. The serum anti-fungus antibody titers measured by the Ouchterlony method were negative for both fungi. The specific IgG and IgE levels for *S. commune* measured by the Phadia CAP system (Phadia Ltd, Uppsala, Sweden)⁹ were revealed to be positive 10.7 (>2.00) mgA/L and 1.34 (>0.35) kIU/L respectively.

Five days after the admission the patient's coughing gradually improved. After suction removal of mucus plugs with a bronchoscope, the patient's chest radiograph showed further resolution.

The results of a pulmonary function test using the Collins DS system¹⁰ and the provocative concentration of methacholine¹¹ that caused a 20% decrease from the baseline FEV₁ (PC20) are summarized in Table 1.

The bronchoprovocation test using *A. niger* antigen was negative; however, the test using *S. commune* antigen was graded as positive due to the development of a coughing attack and a ticklish throat, significant decrease in PaO₂ (from 97.4 to 84.1 mmHg), and in-

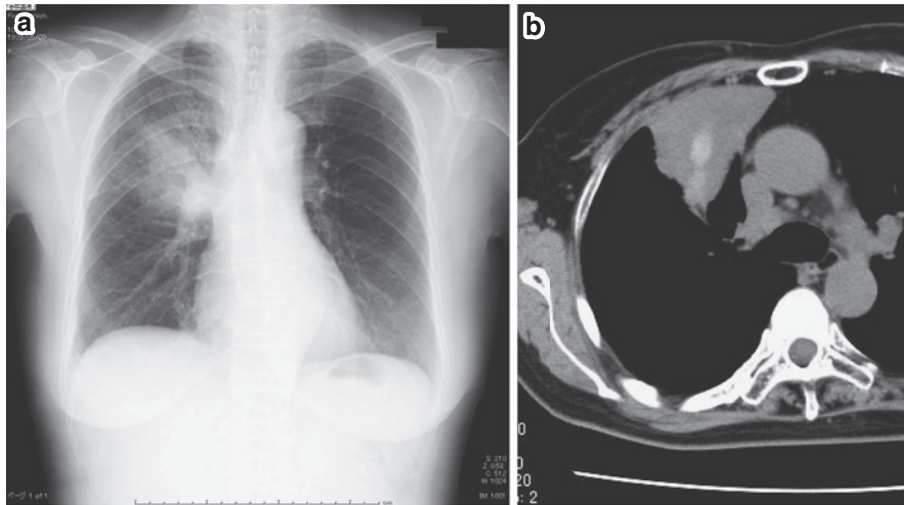


Fig. 2 a: Chest radiographs taken upon admission showing consolidation on the right lung field in Case 2. b: Mediastinal window of computed tomography of the chest showing hyperattenuating mucoid impaction in the right S³.

crease in the serum CRP (from 0.82 to 2.12 mg/dl) on the day following the provocation. These symptoms spontaneously disappeared within 3 days after the challenge.

She experienced no recrudescence after returning home after environmental exposure, and a fungal culture obtained from the floor of the patient's bedroom yielded no significant colonies. Subsequently the patient's coughing had subsided on February 22 and *S. commune* had disappeared from her sputum without any need for the administration of antifungal drugs. The patient has since been healthy without any recurrence of the symptoms during the following 4 years without any need for the use of corticosteroids.

CASE REPORT 2

A 70-year-old female patient was admitted to our hospital on March 28, 2009 for the investigation of a productive cough, high fever, general malaise, and abnormal pulmonary infiltrates. The mucus plug production developed in January 2009 and had not improved. Physical examination revealed a body temperature of 38.0°C and a heart rate of 100 beats per minute. Auscultation did not reveal any abnormalities such as wheezes or rhonchi.

Laboratory tests revealed a white blood cell count of 14,500 per μ l with 9.4% eosinophils. CRP increased to 17.3 mg/dl. A radioimmunosorbent test revealed an elevated total IgE level (787 U/ml), and the radioallergosorbent test for specific IgE antibodies against *Aspergillus*, *Penicillium*, *Candida*, and *Alternaria* were 1.31, 1.83, 1.00, and 0.57 (UA/mL), respectively. A differential cell analysis of sputum revealed marked eosinophilia (1% alveolar macrophages, 22% neutrophils, and 77% eosinophils).

Chest radiographs taken upon admission (Fig. 2a)

showed consolidation on the right lung field. Mediastinal window of computed tomography of the chest showed hyperattenuating mucoid impaction⁸ in the right S³ (Fig. 2b).

Although bronchoscopy did not disclose mucous plugs in the right upper lobe bronchi, many small mucous plugs were gathered by bronchial washing. Histological examinations of the mucous plug samples revealed numerous eosinophils. Transbronchial lung biopsy specimens obtained from the right S² showed intraluminal exudation and septal infiltration of eosinophils. Molecular analysis revealed that the sputum culture samples were *Bjerkandera adusta* (*B. adusta*) and the mucous plugs were *S. commune* and *Candida albicans* (*C. albicans*).

The immediate skin reaction was 12 × 10/28 × 34 for *B. adusta*, 10 × 10/18 × 16 for *C. albicans*, 6 × 6/8 × 6 for *A. fumigatus* and 16 × 20/48 × 60 for *S. commune*. The late (8 hr) skin reactions were positive for only *S. commune* (20 × 20/80 × 150). Additional examination of the immediate skin reaction for *S. commune* was 18 × 14/55 × 40, 14 × 12/37 × 40, 10 × 10/29 × 28, 8 × 8/24 × 22, 6 × 6/16 × 12, and 2 × 2/0 × 0 at concentrations of 10⁻³, 10⁻⁴, 10⁻⁵, 10⁻⁶, and 10⁻⁷ mg/ml, respectively. And the specific IgG and IgE levels for *S. commune* was revealed to be positive (2.84 mgA/L and 3.37 kIU/L respectively).

The patient was initially treated with antibiotics (Sultamicillin tosilate, 3.0 g/day and Ciprofloxacin hydrochloride, 600 mg/day), although marked eosinophilia (21.7%) was present in the peripheral blood. As a result, the antibiotics were discontinued but the patient's cough and high fever gradually subsided and a chest radiograph revealed further improvement in six days following the hospital admission.

Environmental causes were investigated since the

patient experienced a recrudescence a day after first returning home on April 21, specifically the recurrence of dry cough, high fever (38.4°C), increase in the serum CRP (from 0.1 to 4.2 mg/dl), decrease in PaO₂ value (from 106 to 88.0 mmHg) and decrease in eosinophil count in the peripheral blood (13.3 to 3.0% (651.7 to 243.0 per µl)). The patient's coughing and high fever had subsided, and was accompanied by an increase in blood eosinophils (9.2% (432.4 per µl) on April 27 without any therapy).

Though the bronchoprovocation test using *B. adusta* antigen and *C. albicans* were both negative, the results of the bronchoprovocation test using *S. commune* at the concentration of 10⁻⁷ mg/ml was graded as positive due to the development of a coughing attack and a febrile 8 hrs after the inhalation, significant decrease in PaO₂ (from 101.3 to 86.7 mmHg), and increase in the serum CRP (from 0.07 to 4.16 mg/dl) on a day following the provocation. These symptoms spontaneously disappeared within 3 days after the challenge.

As an experimental treatment to prevent hypersensitivity to environmental fungi, we prescribed a low dose of ITCZ⁷ to the patient one day before the 2nd trial of returning home, and the patient did not experience any recrudescence at this time. Thereafter, based on the successful results of the environmental exposure test, the patient was finally discharged from the hospital on May 7. After being discharged from the hospital, the patient was maintained on ITCZ syrup 50 mg/day, which was gradually reduced to alternate-day dosage during a 3-month period and thereafter this medication was terminated without any further need for the administration of corticosteroids.

The patient experienced recrudescence of a productive cough on July 1, 2010. She was afebrile with no significant laboratory findings. Petri dishes with Sabouraud's agar medium were exposed for two hours on the floor of the patient's bedroom, and *S. commune* colonized these plates. Because computed tomography of the patient's chest showed mucoid impaction in the right S³, she underwent bronchoscopic suctioning and flushing on August 17, and has been healthy for the 6 months following the procedure.

PATHOLOGICAL FINDINGS AND DISCUSSION

Invasive infection by basidiomycetous fungi is rare and much of the literature reports have suggested the possible role of basidiospores as airborne allergens.¹²⁻¹⁴ And the reports on ABPM or Allergic fungal sinusitis due to *S. commune* have been increasing in incidence.¹⁵⁻¹⁷

The consistency with the Rosenberg criteria was initially evaluated in the two patients with MIB who were successfully diagnosed to have Sc-ABPM using a diagnostic process that we previously proposed for

allergic fungal respiratory disease.⁵

Four of 7 primary characteristics and 1 of 3 secondary criteria in the Rosenberg criteria were fulfilled in Case 1. Five of 7 primary and 2 of 3 secondary characteristics were filled in Case 2 (Table 1). Therefore, the probable diagnosis of ABPM due to *S. commune* could be determined according to the Rosenberg criteria in both cases. On the other hand, in Case 2, plural eumycetes were cultured from bronchial materials, this case also met the criteria of allergic bronchopulmonary candidiasis¹⁸; such as *C. albicans* in sputum, immediate skin reactivity to the *C. albicans* antigen, precipitating antibodies against *C. albicans* antigen.

The well-known data, such as peripheral blood eosinophilia and elevated serum IgE concentrations included in the Rosenberg criteria,³ indicate that there is an allergological factor involved in the individual's condition, but are not sufficient to demonstrate the presence of an allergic reaction against the identified fungi.

Although positive result of immediate skin reactivity for the specific fungus is an important allergological marker, our preliminary study revealed that the positive ratio of the immediate skin reaction for *S. commune* was 5.5%, 5.6%, 21.4%, and 28.3% in healthy volunteers, mild asthmatics, moderate asthmatics, and severe asthmatics, respectively (unpublished data). Furthermore the positive result of the titer of specific IgG for *S. commune* had been considered to be an allergological marker of hypersensitivity to the fungus, but it was also revealed to be positive in the case of MIB which was independent of hypersensitivity reactions caused by *S. commune* in association with bronchiectasis.¹⁹

Therefore, even if *S. commune* was considered as a probable causative antigen on basis of allergological studies such as the immediate skin reaction and the serum anti-fungus antibody titers, it was difficult to make a definitive diagnosis of Sc-ABPM without accomplishing the fourth step in the definitive diagnostic process. We carried out the bronchoprovocation in accordance with the standardized method for antigen inhalation tests on bronchial asthma and hypersensitive pneumonitis described in 1982.²⁰

Because a severe dual repose to *A. fumigatus* in bronchoprovocation test has been previously reported,²¹ these challenges to *S. commune* had been carried out carefully with a diluted extract based on the skin test titration. When future studies clarify the reliability of some allergological makers as a substitution for the inhalation test which is not commonly used in most clinics, the difficulties associated with diagnosing Sc-ABPM may be resolved.

Secondly, a primary lesion underlying the Sc-ABPM was considered with regard to the clinical manifestations demonstrated in our cases. Although a recent pathological study revealed the presence of

mucus plugs to be the primary lesion related to ABPA,²² this MIB theory does not sufficiently elucidate the mechanisms of the clinical manifestations which were demonstrated in Case 2 either upon admission or environmental exposure.

Both cases presented with eosinophilic bronchitis, but no asthmatic conditions were observed. The existence of mucoid impaction depends on the characteristics of mucus production of each fungus which colonized in the bronchial walls. Continuous inflammation caused by protease products released by intramucus fungi will lead to central bronchiectasis. Therefore, clinical manifestations such as asthma, mucoid impaction, and central bronchiectasis are important when considering the differential diagnosis of such disease, but they are not definitive Sc-ABPM symptoms.

We therefore hypothesized that the allergic reaction such as eosinophilic bronchoalveolitis spreading around the mucus plug was the fundamental condition as a primary lesion underlying the Sc-ABPM²³ based on the assumption that the host was afebrile when allergic reactions induced by *S. commune* are limited to the bronchus area, and these patients tend to become febrile while, on the other hand, their chest radiographs demonstrate consolidations in the lung fields when allergic reactions reach the alveolar area.

This proposed concept of a primary lesion in this disease may elucidate the mechanism of the positive response demonstrated in the bronchoprovocation tests in not only case 2, but also in case 1, which was afebrile, and it enabled two cases of MIB that demonstrated quite different clinical manifestations to be located in the same spectrum of ABPM.

Finally, the successful treatment of Sc-ABPM is herein discussed. In such a situation, the successful treatment is assumed to consist of 4 strategies; 1) the prevention and eradication of fungal colonization in the airway, 2) the control of eosinophilic bronchitis caused by fungal exposure, 3) the removal of any mucus plugs from the airway, and 4) the effective management of environmental fungi.

Gonzalez GM *et al.* reported that *S. commune* was susceptible *in vitro* to ITCZ, amphotericin B, and voriconazole, with MIC values of 0.06 µg/ml, 0.5 µg/ml and 0.5 µg/ml, respectively.²⁴ Therefore, such antifungal therapy may have some advantages²⁵ in either reducing or eradicating such antigen exposure.²⁶⁻²⁸ Because the specimens obtained from transbronchial bronchial biopsy showed no findings of fungal infection in the bronchial wall, it was suggested that ITCZ therapy^{13,26} may be efficacious for preventing the fungi from colonizing the airway upon antigen exposure, which subsequently causes eosinophilic inflammation. It was remarkable that the low dose ITCZ therapy in case 2 successfully prevented relapse upon environmental re-exposure²⁸ and stopped eosinophil

movement²⁹ (Strategy 1). For the treatment of an allergic reaction in the airway which has already been started by the colonization of the fungi, both inhaled and oral corticosteroids are considered to be efficacious³⁰ (Strategy 2). On the other hand, the oral drugs seemed to be more difficult to deliver to the fungus colonizing inside the mucus plug. In the near future, the use of additional therapy, such as nebulized antifungal drugs³¹ should be evaluated for the treatment of the mucus plug. The utility of the bronchoscopic suctioning and flushing as a mechanical treatment has been reported previously^{2,17}; and we also experienced the efficacy of this mechanical treatment (Strategy 3). *S. commune* is a basidiomycetous fungus that colonizes rotting wood, and it is distributed throughout the world. It is known that the quantity of antigen from the basidiomycetous fungi is affected by the season.³² Our case reports suggested that the control of the disease recurrence which seemed to be influenced by the existence of *S. commune* in the environment will be accomplished by the environmental management (Strategy 4).

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CONFLICT OF INTEREST

The authors declare that they have no competing interests that might be perceived to influence the results and discussion reported in the present manuscript.

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