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Case report

Acute respiratory failure due to *Aspergillus niger* infection with acute fibrinous and organazing pneumonia: A case report

Ken Okamura [a], Rintaro Noro [a,*], Kazue Fujita [a], Shoko Kure [b], Shinobu Kunugi [c], Hitoshi Takano [d], Ryota Miyashita [a], Takehiro Tozuka [a], Toru Tanaka [a], Teppei Sugano [a], Yumi Sakurai [a], Ayana Suzuki [a], Miyuri Suga [a], Anna Hayashi [a], Yoshinobu Saito [a], Kaoru Kubota [a], Masahiro Seike [a], Akihiko Gemma [a]

[a] *Department of Respiratory Medicine, Nippon Medical School Hospital, Japan*
[b] *Department of Diagnostic Pathology, Nippon Medical School Musashikosugi Hospital, Japan*
[c] *Department of Pathology, Nippon Medical School Hospital, Japan*
[d] *Department of Cardiology, Nippon Medical School Hospital, Japan*

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ABSTRACT

A 59-year-old woman complaining of wet cough, hemoptysis, slight fever, anorexia, and malaise was admitted to hospital with suspected lobar pneumonia. She received treatment for myocardial infarction and deep venous thrombosis caused by familial protein C deficiency. Rapid deterioration due to respiratory failure occurred despite intensive care with broad-spectrum antibiotics. At a later date, sputum examination revealed the presence of *Aspergillus niger*. Based on clinical and autopsy findings, she was diagnosed with acute respiratory failure due to pulmonary aspergillosis with acute fibrinous and organizing pneumonia. This is the first reported case of pulmonary aspergillosis with acute fibrinous and organizing pneumonia complicated by calcium oxalate resulting from *Aspergillus niger* infection, leading to severe inflammation and tissue injury in the lungs.

1. Introduction

Pulmonary aspergillosis is a disease that often requires predisposing host factors to cause infection. Such factors include prior infections, COPD or other obstructive lung diseases, or structural lung diseases. Typically, *Aspergillus* colonizes lung tissue resulting in ulcers and necrosis, and often has a chronic course (e.g., chronic necrotizing pulmonary aspergillosis). In some cases, however, invasive pulmonary aspergillosis (IPA) can be seen in more acute states, and *Aspergillus fumigatus* infection has been frequently reported. *Aspergillus niger* (*A. niger*) is widely found in the molds of fruits and vegetables; however, reports of infection in humans are rare.

Acute fibrinous and organizing pneumonia (AFOP) is a rare histologic pattern of acute lung involvement with intra-alveolar fibrin deposition, and mainly shows an organizing pneumonia (OP) pattern on high-resolution computed tomography. There are even a few papers on *A. niger* causing non-AFOP organizing pneumonia and plenty of papers that talk about calcium oxalate crystal deposition from *A. niger*. It is reported that calcium oxalate in the lungs causes lung injury, so calcium oxalate crystal deposition from *A. niger* may

* Corresponding author. Department of Pulmonary Medicine and Oncology, Graduate School of Medicine. Nippon Medical School, 1-1-5, Sendagi, Bunkyo-ku, Tokyo, 113-8603, Japan.
E-mail addresses: k-okamura@nms.ac.jp (K. Okamura), r-noro@nms.ac.jp (R. Noro).

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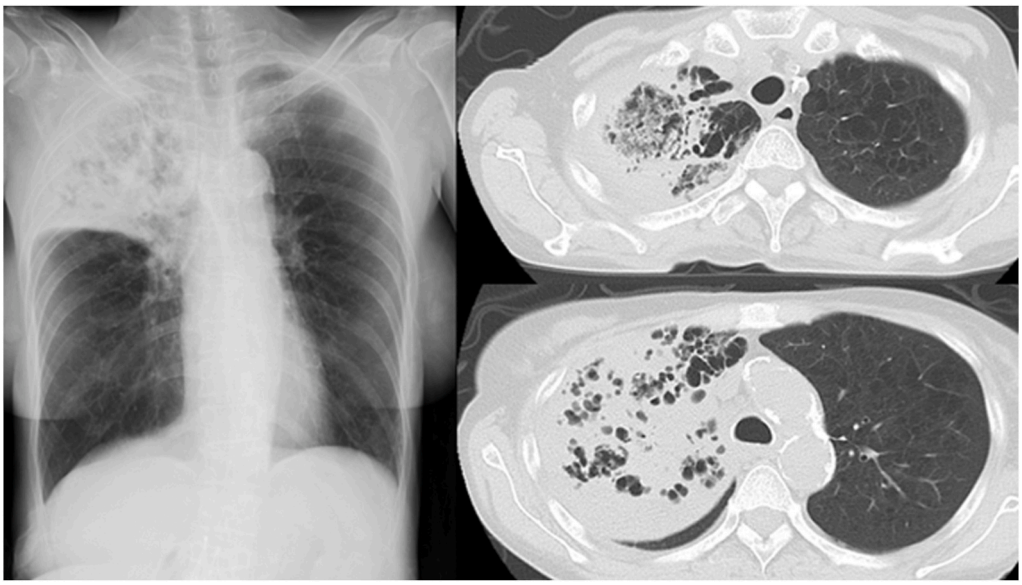

Fig. 1. Chest X-ray examination on admission showed infiltration in the right upper lobe field. Chest computed tomography on admission showed an infiltration shadow with air bubbles in the right upper lobe and severe emphysema in the left lobes.

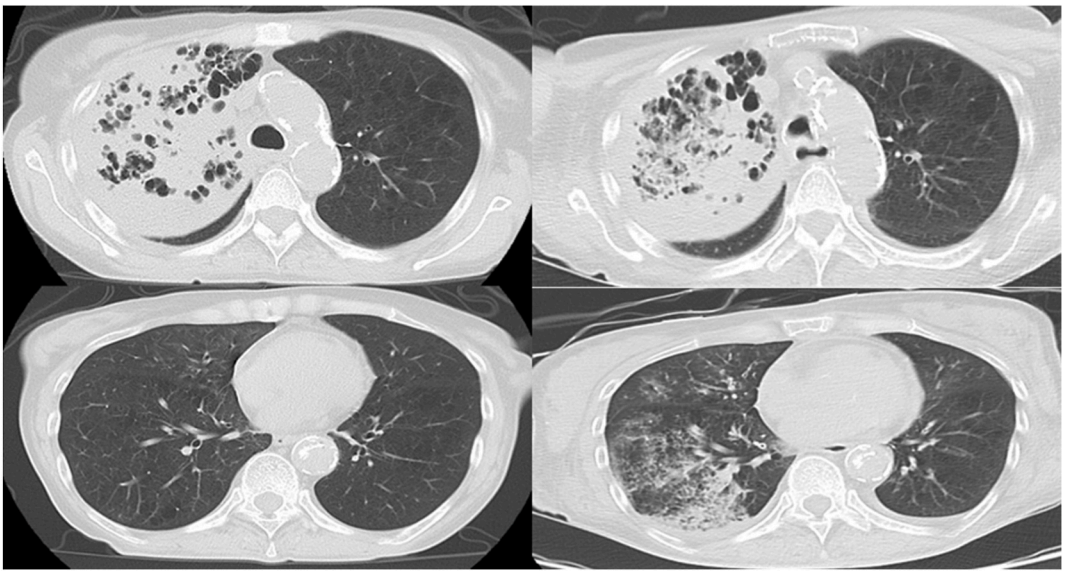

Fig. 2. Chest computed tomography on admission (left side) and at day 4 (right side) showed new infiltration with ground glass opacity in the right lower lobe.

cause non-AFOP organizing pneumonia and AFOP. In addition, thus far, there are no reports of pulmonary aspergillosis associated with AFOP.

In this article, we report the first case of severe pulmonary aspergillosis complicated by deposition of calcium oxalate crystals resulting from *A. niger* infection, leading to rapid respiratory failure due to severe inflammation in the lungs, such as AFOP.

2. Case Report

A 59-year-old woman presented with a 2-week history of wet cough, hemosputum, slight fever, anorexia, and malaise. Chest X-ray examination also showed an infiltration shadow, and the patient was admitted to Department of Respiratory Medicine, Nippon Medical School Hospital. She had a history of pulmonary embolism and myocardial infarction at the age of 35 due to protein C deficiency requiring anticoagulation along with a history of heavy alcohol consumption (500 mL of beer/day), severe emphysema due to heavy smoking (smoking index: 780), and unbalanced diet.

On admission, a physical examination revealed the following: body mass index 16.4; temperature 37.2 °C; and arterial oxygen

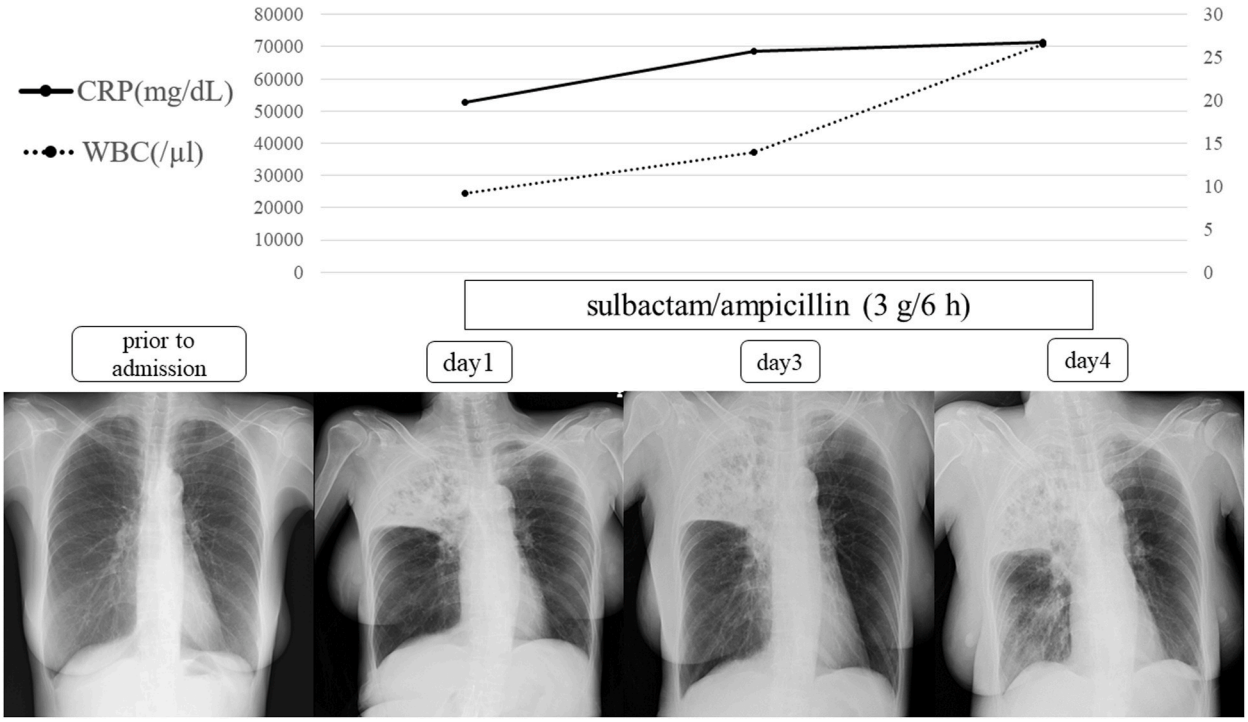

Fig. 3. Despite having been treated with sulbactam/ampicillin, laboratory findings such as white blood cells (WBC) and C-reactive protein (CRP) got worse. Chest X-ray examination showed that infiltration in the right upper lobe field remained and new infiltration appeared in the right lower lobe.

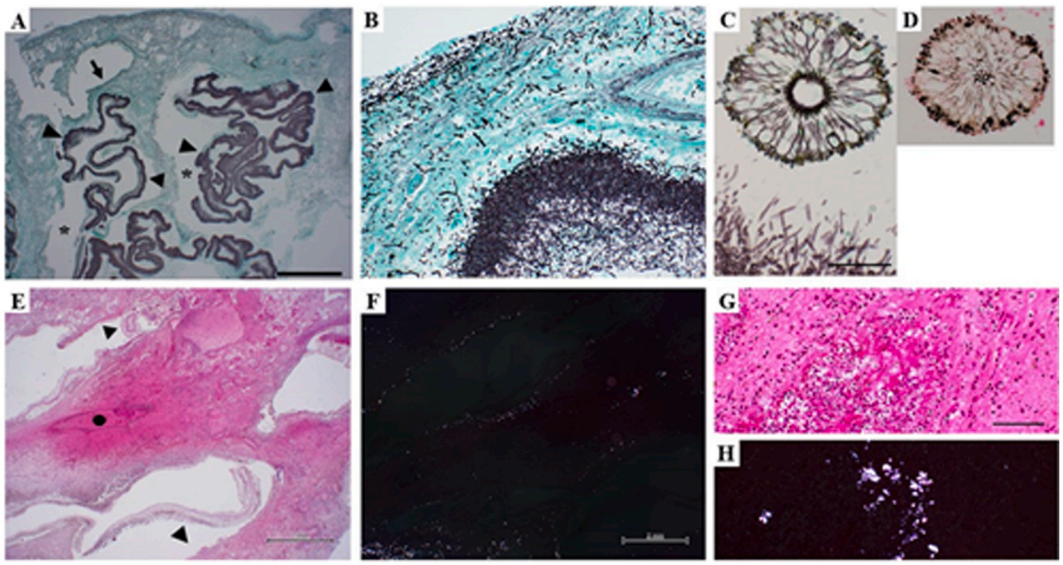

Fig. 4. Autopsy findings of the right upper lobe. (**A**) Grocott's staining showed micronodular fungal masses (asterisk) in dilated air spaces (arrow heads) (bar: 2 mm). (**B**) Grocott's staining revealed branching septate hyphae compatible with *Aspergillus* spp. with parenchymal invasion adjacent to a micronodular fungal mass (bar: 100 μm). (**C**) Fruiting head within the fungal mass, Grocott's staining (bar: 50 μm). (**D**) Fontana–Masson staining showed strong intensity in the peripheral area of the fruiting head. (**E**) In some areas of the right upper lobe, hemorrhagic and necrotic areas were observed (black circle, pulmonary artery [PA]; arrow heads: fungus; bar: 2 mm). (**F**) Numerous birefringent crystallin structures with polarized light consistent with calcium oxalate deposition were observed in the same area with E (bar: 2 mm). (**G**) High magnification of PA showed the presence of fibrin thrombi with neutrophil infiltration (bar: 100 μm). (**H**) calcium oxalate deposition was noted in the PA wall.

saturation of pulse oxymetry 96%. Laboratory findings were as follows: arterial blood gas test without oxygen administration; pH 7.529; partial pressure of CO_2 28.5 mmHg; partial pressure of O_2 72.4 mmHg; HCO3- 23.2 mEq/L; white blood cells 24,400/mm^3; neutrophil count 22,545/mm^3; lymphocyte count 756/mm^3; hemoglobin 9.7 g/dL; platelets 36.4 $\times$ 10^4/mm^3; serum total protein 6.1

g/dL; albumin 1.8 g/dL; creatinine 0.43 mg/dL; blood urea nitrogen 5.9 mg/dL; prothrombin time-international normalized ratio 1.4 μg/mL; D-dimer 4.4 μg/mL; aspartate transaminase 73 U/L; alanine transaminase 63 U/L; sodium 124 mmoL/L; potassium 3.8 mmoL/L; C-reactive protein 19.81 mg/dL; N-terminal pro-brain natriuretic peptide 735.3 pg/mL; hemoglobin A1c 6.8%; and β-D-glucan 6.7 pg/mL. Chest X-ray examination on admission showed infiltration in the right higher lung field. Chest computed tomography on admission showed lobular consolidation with air bubbles in the right upper lobe and severe emphysema in both right and left lobes (Fig. 1).

X-ray examination prior to admission demonstrated maintained lung permeability. Nevertheless, on day 1, a segmental infiltrative shadow with aeration appeared in the right upper lung field. At the time of admission, the respiratory condition was stable without oxygen administration, and administration of sulbactam/ampicillin (3 g/6 h) as empiric therapy was initiated. On day 3 of hospitalization, the sputum culture did not show bacterial growth, including indigenous bacteria, except for *A. niger*. Permeability of segmental infiltrates decreased on days 3 and 4, new infiltrates appeared in the right lower lung field (Fig. 2). Laboratory findings such as white blood cells and C-reactive protein increased, and the oxygen level tended to gradually decrease (Fig. 3). On day 4, The patient suddenly suffered from impaired consciousness and needed more oxygen, and then expired because of acute respiratory failure.

Autopsy findings showed micronodular fungal masses within emphysematous air-space enlargement in the right upper lobe (Fig. 4A). Grocott's staining showed abundant branched filamentous hyphae, suggesting *Aspergillus* infection and parenchymal invasion (Fig. 4B). These findings were consistent with chronic necrotizing aspergillosis. Fruiting bodies were observed within the fungal mass. Fontana–Masson staining revealed positive intensity and peripheral pigmentation indicating melanin (Fig. 4D and E). In some areas of the right upper lobe, hemorrhage and necrotic change were noted with birefringent crystallin structure with polarized light (Fig. 4F). There were numerous calcium oxalate crystals in the pulmonary arterial wall with fibrin deposition and neutrophil infiltration (Fig. 4G and H). The presence of fruiting bodies combined with oxalate crystals is highly suggestive of *A. niger* infection and was consistent with the results of the sputum test. AFOP was observed in the peri micronodular fungal mass without fungal infection. Intrahepatic neutrophil infiltration, splenitis, and hyperplastic bone marrow were observed, suggesting systemic inflammation due to *Aspergillus* infection.

Previously recorded myocardial infarction, deep vein thrombosis, right renal infarction, and aortic wall thrombosis were observed. However, a new thrombosis that could cause respiratory failure was not detected.

3. Discussion

In this case, the patient had deep vein thrombosis and myocardial infarction due to protein C deficiency, COPD, and alcohol consumption. Therefore, it is considered that COPD and the malnutrition-induced leanness due to those factors caused *Aspergillus* infection. Pathological autopsy revealed Y-shaped hyphae from the lung lesions. In addition, a blackish-brown Fontana–Masson-positive pigment was found in the periphery of the fruiting body, which was identified as *A. niger*. Pathological findings revealed that *A. niger* was mainly detected in the upper right lobe. However, extensive AFOP that showed Intra-alveolar fibrin and polypoid fibrosis was observed in the entire right lung, whereas inflammation and OP were not observed in the left lung. Calcium oxalate deposition was noted with vascular injury.

Aspergillus is a common filamentous environmental fungi; there are approximately 200 species, less than 20 of which are pathogenic to humans [1]. Microscopic conidia that are incidentally inhaled are normally excreted from the lung when they reach to the respiratory tract and the alveoli. Healthy individuals often do not become infected due to neutrophilic killing activity against any conidia that manage to germinate into hyphal forms. However, following a decrease in local defense (e.g., formation of cavitary lesions in the lungs, immunodeficiency, or neutropenia), the fungus can cause chronic infection. It has been shown that patients with severe immunodeficiency (e.g., persistent neutropenia, steroid therapy, hematopoietic stem cell transplant recipients, acquired immunodeficiency syndrome, chronic granulomatosis, and severely pulmonary structural destruction) are susceptible to the development of IPA [2,3]. There are also reports that COPD and severe influenza morbidity can increase the risk of developing IPA, even in patients without clear immunosuppression [4,5]. *Aspergillus fumigatus* is the most common causative agent of IPA, and there is a limited number of reports of *A. niger* as a trigger. A cohort study of patients with hematological disorders showed that only 4% of 194 IPA cases were caused by *A. niger* [6]. In chronic progressive pulmonary aspergillosis (CPPA), the cavity wall is characterized by destructive lesions (e.g., ulcers and necrosis). However, no alveolar tissue or intravascular invasion is observed [7]. In 1981, Wehmer discovered that *A. niger* produces oxalic acid. The produced oxalic acid reacts with extracellular fluid and blood, and deposits as calcium oxalate. Calcium oxalate deposits are rarely found in individuals with other types of *Aspergillus*, and are hallmarks of *A. niger* infection. Black pigments scattered around the fruiting body are another characteristic of *A. niger* [8]. In animal experiments, rats were intratracheally inoculated with *A. niger* following the administration of an immunosuppressive drug. The results demonstrated that lung injury is caused by calcium oxalate (pulmonary oxalosis) rather than the invasion of *A. niger* itself [9]. In a case of alveolar hemorrhage in a patient infected with *A. niger*, the tissue and vascular invasion by *A. niger* was negative, suggesting the involvement of calcium oxalate [10]. Moreover, in a patient with bilateral infiltrative shadows, *A. niger* was localized in only one lung. Furthermore, deposition of calcium oxalate was observed in the pathological autopsy results of patients infected with *A. niger* [11]. Generally, the progression of CPPA is slow and rarely follows the course of rapid respiratory failure. Following the progression of structural destruction toward a lung lesion, it is difficult to suspect the presence of IPA. However, from the pathological view, it was surprising that rapid respiratory failure occurred despite the localized infection. A fungus ball was formed in the cystic change, which later became invasive and was accompanied by necrosis. AFOP spread widely around the invasion site, and crystal deposition was conspicuous; however, organization was also observed in places where fungi or crystals were not present (Fig. 5). Based on these pathological autopsy findings, it was considered that respiratory failure was the result of AFOP due to calcium oxalate deposition caused by *A. niger*.

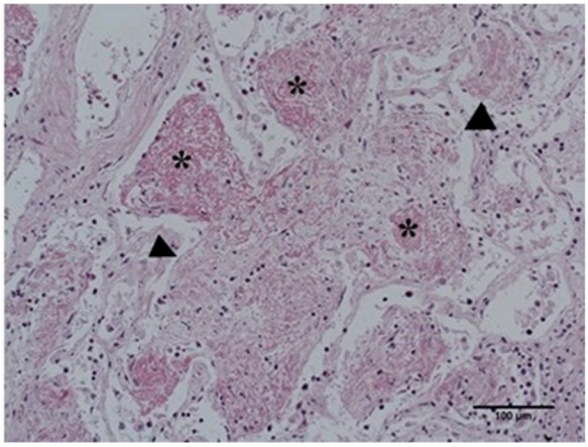

Fig. 5. Intra-alveolar fibrin (*) and polypoid fibrosis (arrow heads) indicating acute fibrinous and organizing pneumonia. Hematoxylin–eosin staining, bar: 100 μm.

AFOP is a rare histologic pattern of interstitial lung disease characterized by intra-alveolar fibrin balls and OP with a patchy distribution [12]. It is pathologically classified and mainly shows an OP pattern on high-resolution computed tomography. It is associated with several diseases, such as infection (e.g., *Haemophilus influenza, Acinetobacter*), autoimmune diseases (e.g., anti-neutrophil cytoplasmic autoantibody-associated vasculitis, rheumatoid arthritis, polymyositis/dermatomyositis, scleroderma), radiation pneumonitis, drug-induced pneumonia, hematologic diseases, and IgG4-related disease [13]. In some reports of pulmonary aspergillosis with OP, combination therapy with antifungal agents and corticosteroids was effective [14,15]. In certain cases, pulmonary aspergillosis with OP was caused by *A. niger* [14,16,17]. Although corticosteroids are effective against AFOP, the rate of recurrence is higher than that of cryptogenic organizing pneumonia and nonspecific interstitial pneumonia [13]. Though we had no time to attempt to evaluate the effects of antifungal therapy and corticosteroids in this case, it is suggested that calcium oxalate deposition by *A. niger* causes lung injury, such as OP and AFOP, and that the aforementioned combination therapy may be effective against pulmonary aspergillosis with AFOP.

4. Conclusion

We reported the first case of pulmonary aspergillosis presenting with AFOP associated with pulmonary oxalosis due to *A. niger* infection. Numerous *Aspergillus* infections often follow a chronic course. However, when *A. niger* is the causative agent, rapid severe respiratory failure may develop due to the tissue damage associated with calcium oxalate deposition. The early diagnosis of pulmonary aspergillosis with AFOP and identification of appropriate treatment warrant further investigation in the future.

Author contributions

Conceptualization, writing and editing – original draft preparation: Ken Okamura and Rintaro Noro. Investigation: Kazue Fujita, Shoko Kure, Shinobu Kunugi, Hitoshi Takano, Ryota Miyashita, Takehiro Tozuka, Yumi Sakurai, Ayana Suzuki, Miyuri Suga, Anna Hayashi, Toru Tanaka, Teppei Sugano Review: Yoshinobu Saito, Kaoru Kubota, Masahiro Seike and Akihiko Gemma.

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Declaration of competing interest

The authors declare that they do not have any conflict of interest.

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