



Case report

Acute exacerbation of airspace enlargement with fibrosis



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A B S T R A C T

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In 2008, Kawabata et al. described a lesion which they termed “airspace enlargement with fibrosis” that could be included on the spectrum of smoking-related interstitial lung diseases. This group also reported that patients with airspace enlargement with fibrosis but without coexisting interstitial pneumonia of another type had no acute exacerbations and favorable prognoses on clinical follow-up. Here we describe the first case, to our knowledge, of acute exacerbation of airspace enlargement with fibrosis without coexisting interstitial pneumonia of another type. An 82-year-old man was referred to our department for worsening dyspnea and new alveolar opacities on chest radiograph following left pulmonary segmentectomy (S6) for cancer. A diagnosis of acute exacerbation of airspace enlargement with fibrosis without coexisting interstitial pneumonia of other types was made, based on pathological evidence of airspace enlargement with fibrosis and organizing diffuse alveolar damage. Treatment with high-dose methylprednisolone followed by tapered oral prednisolone resulted in gradual improvement of the clinical condition and chest radiographic findings. Clinicians should be aware that patients with airspace enlargement with fibrosis may experience acute exacerbation.

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Introduction

Smoking is associated with chronic obstructive pulmonary diseases and lung cancer. Recently smoking has been implicated as a cause of interstitial lung disease, in what is called “smoking-related interstitial lung disease” [1–5]. It has been reported that pathologically significant but clinically unrecognized interstitial fibrosis occurs commonly in cigarette smokers [1–5]. In 2008, Kawabata et al. [6] described a lesion which they termed “airspace enlargement with fibrosis (AEF)” that could be included on the spectrum of smoking-related interstitial lung diseases. The lesion is

frequently located in a bronchiolocentric location in the setting of emphysema, and is characterized by a fibrous and frequently hyalinized interstitium with structural remodeling, but lacking foci of fibroblasts. These incidental histologic findings in smokers are not regarded as a distinct form of idiopathic interstitial pneumonia (IIP) [5], but AEF includes more interstitial fibrosis than described for the classic definition of emphysema [7]. Yamada et al. [8] suggested that the histological features of AEF differed significantly from usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), and centrilobular emphysema (CLE) and that the mechanism of fibrosis of AEF is different from that of UIP and NSIP. They also reported that patients with AEF but without coexisting interstitial pneumonia of another type had no acute exacerbations and favorable prognoses on clinical follow-up [6,8]. They speculated that their observation suggested that the AEF and UIP patterns might be fundamentally different, perhaps related to the fact that foci of fibroblasts are not a feature of AEF [6]. However, the natural disease course of AEF has not been fully understood.

Here we describe an AEF patient without coexisting interstitial pneumonia of another type in whom the natural disease course and sequential changes on chest high-resolution computed

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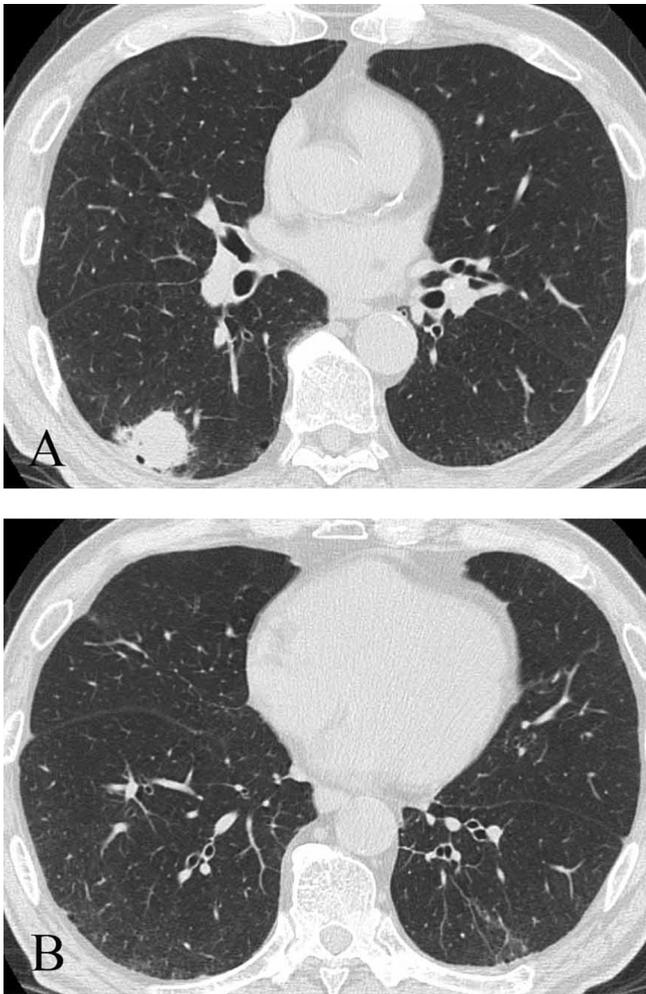


Fig. 1. High-resolution computed tomography (HRCT) before the first surgery. HRCT of the chest revealed a nodule in the right lower lobe (A) and ill-defined centrilobular small nodules and ground-glass opacities, in addition to low attenuation areas and small cysts, in the subpleural areas bilaterally (B).

tomography (HRCT) findings were precisely observed, and who finally experienced acute exacerbation. To our knowledge, this is the first reported case of acute exacerbation of AEF in a patient without coexisting interstitial pneumonia of another type.

Case report

An 82-year-old man was referred to our department for worsening dyspnea and new alveolar opacities on chest radiograph

following left lung segmentectomy (S6). He was an ex-smoker (20 cigarettes a day for 57 years) who had quit smoking 5 years previously. He had been diagnosed with squamous cell carcinoma of the lung 4 years previously and had undergone combined right middle and lower lobectomies (first surgery). Before the first surgery, HRCT of the chest revealed ill-defined, centrilobular, small nodules and ground-glass opacities (GGOs), in addition to low attenuation areas and small cysts, in the subpleural areas bilaterally (Fig. 1). However, 20 months after the first surgery, GGO appeared along the subpleural area of the right residual lung on HRCT and gradually changed to consolidation with bronchiectasis (Fig. 2). Subsequently, 3 years after the first surgery, HRCT revealed a new nodule in the left lower lobe (S6) that gradually increased in size, suggesting the possibility of recurrence of the lung cancer. Therefore, he underwent segmentectomy (S6) of the left lung 4 years after the first surgery. Interstitial opacities were not evident in the left lung on HRCT 2 months before that second surgery. Consolidation with bronchiectasis was evident along the subpleural area in the right residual lung (Fig. 3). The chest radiograph obtained before the second surgery showed no GGOs in the left lung (Fig. 4). The patient did not complain of worsening dyspnea before the second surgery, and the respiratory status was stable before, during, and just after that procedure. The patient presented to our department 10 days after the second surgery complaining of worsening dyspnea for 2 days. There was no history of exposure to any infectious, toxic, or environmental agent that could cause interstitial lung disease. Physical examination revealed that he was afebrile. Fine crackles were detected bilaterally on chest auscultation. Results of arterial blood gas analysis on 2 L/min O₂ via nasal cannula were pH 7.468, PaO₂ 83.9 Torr and PaCO₂ 36.0 Torr. Laboratory examinations on admission revealed a white blood cell count of 12,800/mm³ with 90% neutrophils. C-reactive protein was elevated (6.43 mg/dL). Serum lactate dehydrogenase level was elevated (426 IU/L). Serum Krebs von den Lungen-6 (KL-6) and surfactant protein-D levels were elevated (881 U/mL and 717 ng/mL, respectively). Anti-nuclear antibody and other autoantibodies to specific antigens were all negative. Pneumococcal and *Legionella* urinary antigens were negative. Cultures of blood to detect bacteria, fungi, and mycobacteria were all negative. Results of serological tests for *Mycoplasma pneumoniae*, *Chlamydomphila pneumoniae*, and *Chlamydomphila psittaci* were negative; test results for β-D glucan and cytomegalovirus antigen were also negative. Echocardiography demonstrated no evidence of heart failure. Chest radiograph showed bilateral GGOs in both lower lung fields (Fig. 5). HRCT showed bilateral non-homogenous GGOs with traction bronchiectasis and bronchiolectasis with basilar predominance (Fig. 6). The left lung S6 segmentectomy tumor specimens contained pleomorphic carcinoma that had components of sarcomatoid carcinoma and adenocarcinoma. The surrounding, uninvolved area had emphysematous changes with interstitial and peribronchiolar fibrosis, but without histological features of IIPs, such as UIP or NSIP

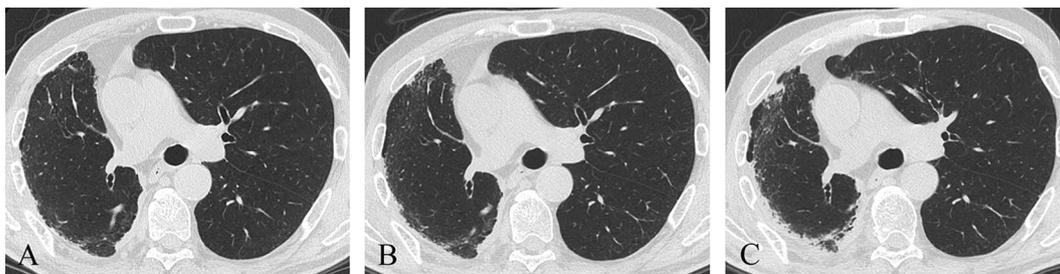


Fig. 2. High-resolution computed tomography (HRCT) after the first surgery. Ground-glass opacities appeared along the subpleural area of the right residual lung 20 months after the first surgery (A), and then gradually changed to consolidation with bronchiectasis on HRCT: 26 months after the first surgery (B); 38 months after the first surgery (C).

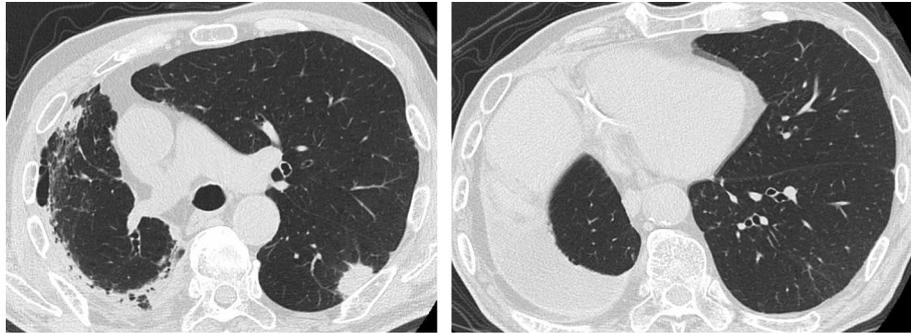


Fig. 3. High-resolution computed tomography (HRCT) 4 years after the first surgery (2 months before the second surgery). HRCT of the chest revealed a new nodule in the left lower lobe (S6). Interstitial opacities were not evident in the left lung. Consolidation with bronchiectasis was evident along the subpleural area of the right residual lung.

patterns, indicating presence of AEF. Also observed were polypoid fibrosis in alveoli and respiratory bronchioles, focal hyaline membranes, epithelial denudation, and focal squamous metaplasia, suggesting organizing diffuse alveolar damage. Retrospective analysis of the previous specimens of the right middle and lower lobes resected during the first surgery revealed AEF without any histological features of IIPs (Fig. 7). Based on these findings, a diagnosis of acute exacerbation of AEF was made. The patient was treated with high-dose methylprednisolone (1 g/day intravenously for 3 days) followed by oral prednisolone (40 mg/day). Chest HRCT performed 2 weeks later showed some improvement of the GGOs (Fig. 8). Oral prednisolone was then tapered off very gradually, by 5 mg/day every 2 weeks to 20 mg/day, and then by 2.5 mg/day every 2 weeks to 12.5 mg/day. This resulted in a gradual improvement of the clinical condition and the chest radiographic findings. However, chest HRCT revealed a new nodule in the left lower lobe and left pleural effusion 2 months after the second surgery, suggesting the possibility of recurrence of lung cancer and

malignant left pleural effusion. The patient died 4 months after the second surgery. There was no further episode of acute exacerbation of AEF during the clinical course.

Discussion

To our knowledge, this is the first reported case of acute exacerbation of AEF without coexisting IIPs (pure AEF). Acute exacerbation of idiopathic pulmonary fibrosis (IPF) can be identified by an unexplainable increase in dyspnea symptoms within 1 month of onset; a deterioration in gaseous exchange indicating hypoxemia; new radiographic alveolar infiltrates; and by ruling out other possibilities such as infection, pulmonary embolism, pneumothorax, or heart failure [9]. The present case met these criteria, and diffuse alveolar damage was observed in the lung specimen resected during the second surgery, suggesting that the acute exacerbation process had already begun. Accordingly, this case was thought to be an acute exacerbation of AEF rather than acute lung injury/acute respiratory distress syndrome following surgery.

Acute exacerbation of IPF usually progresses rapidly and often results in a fatal outcome [10,11]. In contrast, the response to the

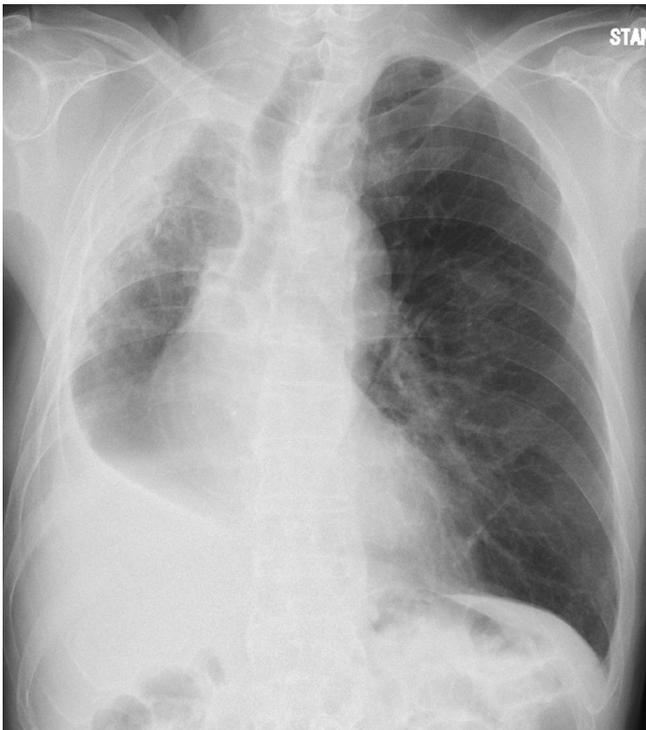


Fig. 4. Chest radiograph before the second surgery. The chest radiograph before the second surgery showed no ground-glass opacities in the left lung.

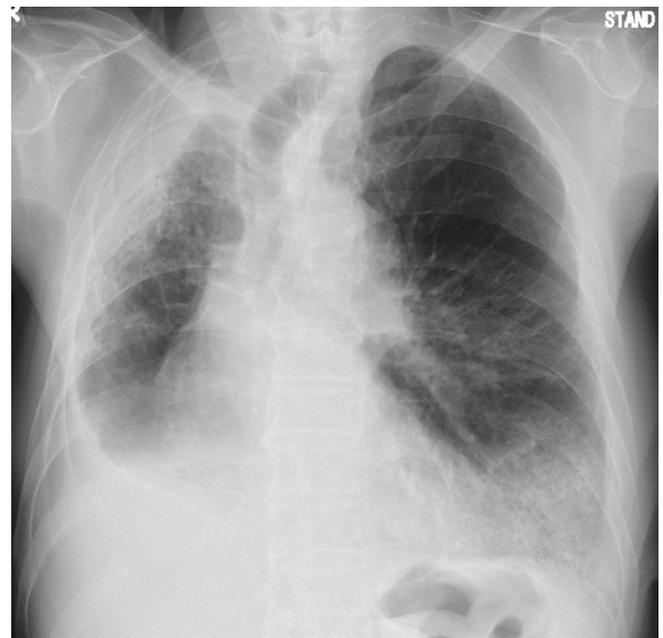


Fig. 5. Chest radiograph 10 days after the second surgery. Chest radiograph showed bilateral ground-glass opacities in the lower lung fields.

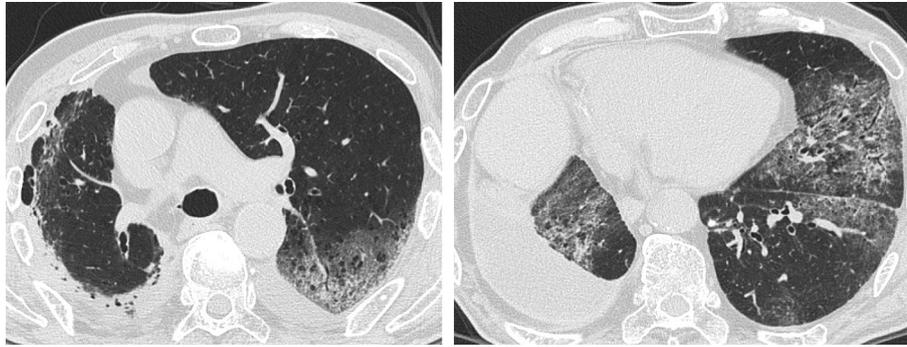


Fig. 6. High-resolution computed tomography (HRCT) 10 days after the second surgery. HRCT of the chest showed bilateral non-homogenous ground-glass opacities with traction bronchiectasis and bronchiolectasis with basilar predominance.

glucocorticoid treatment was relatively good in the present case. The clinical course of the present case suggests that the clinical manifestations of acute exacerbation of pure AEF are different from those of acute exacerbation of IPF. Recent data have suggested that acute exacerbation of IPF may be due to an acceleration of the underlying fibroproliferative disease process [12,13]. Although the

precise mechanisms of the acute exacerbation remain uncertain, the current case suggests that pure AEF could not be categorized simply as CLE, but could be categorized as interstitial lung disease.

Kawabata et al. [6] speculated that AEF might be a subclinical manifestation of a lesion that, when more widespread, presents as clinically apparent interstitial lung disease. They speculated that

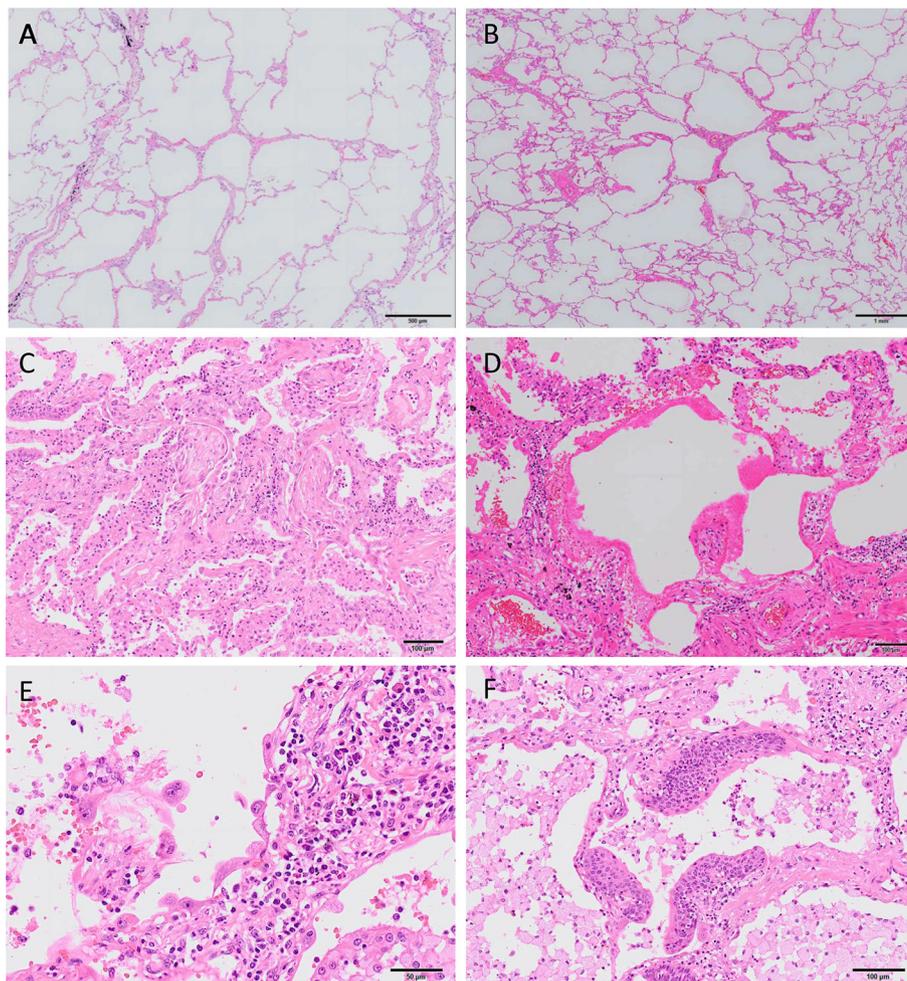


Fig. 7. Histopathological findings (A) Photomicrograph of lung specimen resected during the first surgery. Emphysematous changes with interstitial and peribronchiolar fibrosis, indicating airspace enlargement with fibrosis (AEF) (A, Scale bar = 500 μ m). (B–F) Photomicrographs of lung specimens resected during the second surgery. The non-tumor resected area consisted of emphysematous changes with interstitial and peribronchiolar fibrosis, indicating AEF (B, Scale bar = 1 mm). There are some areas of polypoid fibrosis in alveoli and respiratory bronchioles (C, Scale bar = 100 μ m), focal hyaline membranes (D, Scale bar = 100 μ m), epithelial denudation (E, Scale bar = 50 μ m), and focal squamous metaplasia (F, Scale bar = 100 μ m), suggesting organizing diffuse alveolar damage.

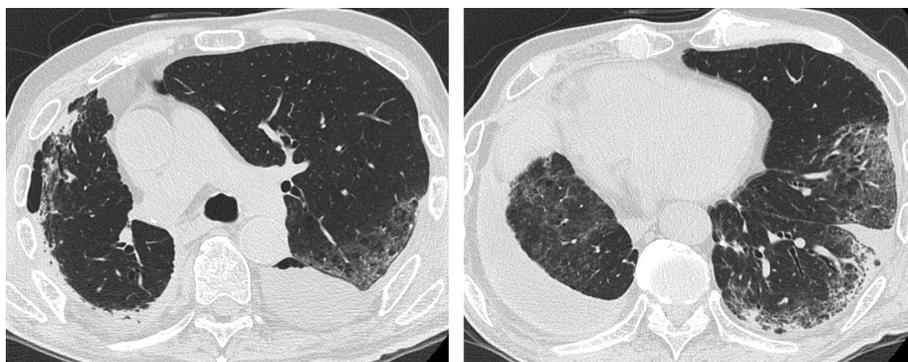


Fig. 8. High-resolution computed tomography (HRCT) 2 weeks after the initiation of corticosteroid therapy. HRCT of the chest obtained 2 weeks after initiation of corticosteroid therapy showed some improvement of ground-glass opacities.

there might be a common mechanism of tissue damage in AEF and CLE, but that fibrosis develops in the former. In the current case, GGO appeared along the subpleural area of the right residual lung on HRCT 20 months after the first surgery, and this gradually changed to consolidation with bronchiectasis, which is consistent with their speculation. However, it is also possible that the HRCT findings reflected a combination of AEF and other types of interstitial pneumonia, because it was reported that AEF and UIP may coexist [6]. However, the HRCT findings of the current case were not typical of UIP, and the changes were seen only in the right residual lung. In addition, histopathological features of the resected lung from the first and second surgeries did not include any evidence of IIPs. Overdistention of the right residual lung due to the combined middle and lower lobectomies could cause stress and strain within the lung and might have accelerated the fibrosis in the right residual lung only. Therefore, it is conceivable that the current case manifested the natural disease course of pure AEF, although this is difficult to prove due to the lack of pathological evidence in the right residual lung.

In conclusion, here we describe what we believe is the first reported case of acute exacerbation of pure AEF. Clinicians should be aware that any patient with AEF may experience acute exacerbation.

Consent

Because the patient was deceased, written informed consent was obtained from his wife for publication of this case report and any accompanying images.

Authors' contributions

TK and KT were involved in drafting the article. TK and DO participated in the diagnosis and treatment of this patient. KT and JF made substantial contributions to the pathological diagnosis. TT and TN participated in the oncology surgery for this patient. SH, NS, YI, KA and SK were involved in critically revising the article for

important intellectual content. All authors read and approved the final manuscript.

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