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Letter to the Editor

An exacerbation of severe asthma with fungal sensitization successfully treated with voriconazole via a reduction of the fungal burden

Dear Editor,

Fungal sensitization is a risk factor for severe asthma. Severe asthma with fungal sensitization (SAFS) is an asthma phenotype first described by Denning *et al.*¹ SAFS patients are poorly controlled, despite combination treatment with high-dose inhaled corticosteroid (ICS)/long acting β_2 agonists (LABAs) therapy. Thus, the efficacy of antifungal therapy has been investigated to reduce causative allergens. Itraconazole (ITCZ) has been reported to improve the quality of life and lung function, and reduce the serum immunoglobulin E (IgE) level.² However, as its clinical trial was conducted in the maintenance phase, the efficacy of antifungal therapy for an exacerbation of asthma is unclear. We report the successful treatment of an exacerbation of asthma in a SAFS patient complicated with *Aspergillus* bronchitis using voriconazole (VRCZ), a potent second-generation triazole antifungal agent.

An 83-year-old woman was admitted to our hospital due to an exacerbation of asthma. She was a never smoker and had no history of respiratory disease other than asthma. The diagnosis of asthma was made at 35 years of age. Her asthma control was poor, and systemic corticosteroids (SCSs) have been administered for over 50 years. A pulmonary function test performed at 72 years of age revealed airflow limitation (% predicted PEF, 47%; FEV1/FVC, 69%). She had been treated with a high-dose ICS (fluticasone, 1000 μ g/day), LABAs, theophylline, an anticholinergic agent, leukotriene receptor antagonists (LTRAs) and low-dose oral corticosteroids (OCSs) (triamcinolone 4 mg/day). Nevertheless, the patient continued to daily exhibit asthma symptoms, such as wheezing, cough, chest tightness and sleep disturbance, for one month before her admission. A physical examination revealed a body temperature of 36.3 °C and an oxygen saturation of 97% (fraction of inspiratory oxygen, 32%). Bilateral wheezing was heard on auscultation. The wheezing fluctuated during the day. Chest computed tomography revealed bronchial wall thickening with a peribronchiolar nodular shadow in both lungs. There was no evidence of bronchiectasis or mucous plugs (Fig. 1). Laboratory tests revealed a white blood cell count of 23,400/ μ L (neutrophil, 93%; eosinophil, 0%), a serum C-reactive protein level of 1.05 mg/dL. Her serum brain natriuretic peptide level was 32.4 pg/ml.

On admission, an exacerbation of asthma complicated by bacterial bronchitis was diagnosed. We increased the dose of SCSs

(betamethasone 8 mg/day) and initiated clarithromycin (CAM; 400 mg/day) as an empiric therapy. Despite these treatments, her condition did not improve, and her wheezing persisted. On the 4th hospital day, CAM was switched to levofloxacin (LVFX; 500 mg/day), based on the antibiotic spectrum. On the 13th hospital day, a diagnosis of SAFS was made based on a serum IgE level of 388.9 IU/ml and an elevated *Aspergillus*-specific IgE titer (class 4). The patient did not meet any of the currently available diagnostic criteria for ABPA. IgE-sensitization to other respiratory allergens was not detected. The diagnosis of *Aspergillus* bronchitis was made based on the serum positivity for *Aspergillus galactomannan* antigen and *Aspergillus* IgG antibody, patient's β -D-glucan level (300 pg/ml) and repeated positive sputum cultures of *Aspergillus fumigatus*. We then switched LVFX to VRCZ (400 mg/day). Three days after initiating VRCZ treatment, the wheezing completely disappeared on auscultation (Fig. 2). She was gradually weaned off of SCSs and discharged on the 31st hospital day. Antifungal therapy was continued for two years (until the present time). Examinations performed two years after the initiation of antifungal therapy revealed that her β -D-glucan and total serum IgE levels had decreased to 31.8 pg/ml and 32.4 IU/ml, respectively, her CT findings improved (Fig. 1), and her sputum cultures changed to negative.

We described a SAFS patient complicated with *Aspergillus* bronchitis who developed an exacerbation of asthma and was successfully treated with VRCZ. Treatment with high-dose SCSs is a fundamental strategy for managing exacerbations of asthma. However, this condition is not always easily treated with high-dose SCSs. In particular, in SAFS, high-dose SCSs may increase the fungal burden, leading to a condition that is refractory against conventional treatments. In fact, it was reported that individuals receiving corticosteroid therapy have significantly higher loads of fungus in their lungs than those not receiving steroid therapy.³ In this respect, antifungal therapy may be more important in cases of exacerbations of asthma. Interestingly, in the current case, the patient had *Aspergillus* bronchitis with a high β -D-glucan level, implying the presence of a high fungal burden. Antifungal therapy may have been particularly effective in our case because of the presence of a high fungal burden, as the impact of the allergen on allergic diseases generally increases with an increasing allergenic load.

Antifungal therapy reduces allergen exposure directly by killing viable filamentous fungi. Some immunologic effects of azoles have also been reported *in vitro*. ITCZ was reported to suppress type 2 cytokine production (interleukin-4 [IL-4] and IL-5) in T cells.⁴

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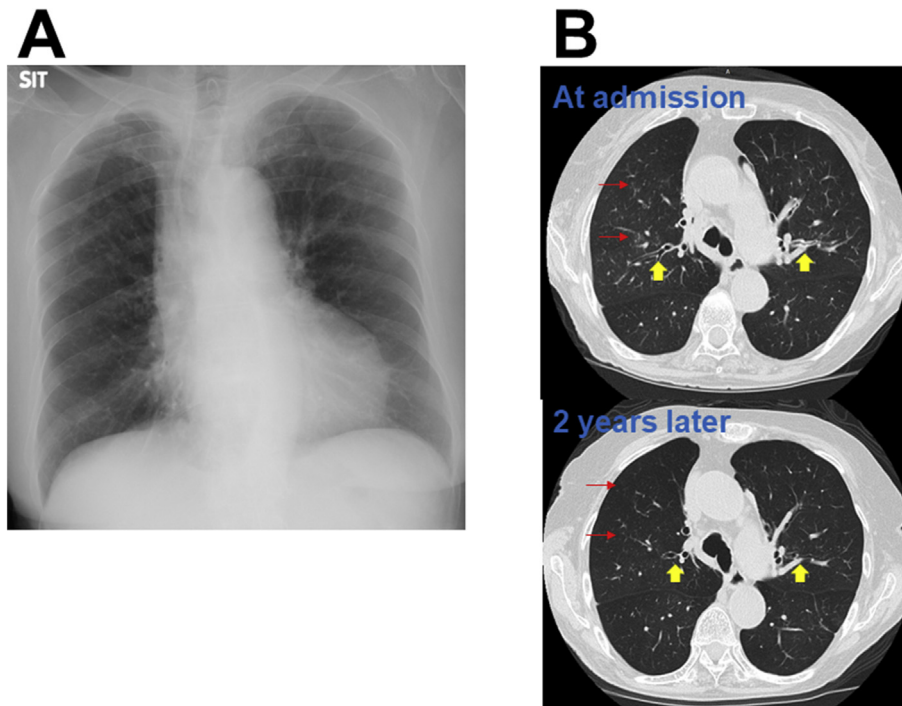


Fig. 1. The Chest X-ray and computed-tomography (CT) findings. **(A)** Chest X-ray showed no abnormal shadows. **(B)** Chest CT revealed bronchial wall thickening in both lungs (yellow arrows) and a peribronchiolar nodular shadow in the right lobe (red arrows). There were no signs of bronchiectasis or mucous plugs. After two years, the bronchial wall thickening and peribronchiolar nodular shadow disappeared.

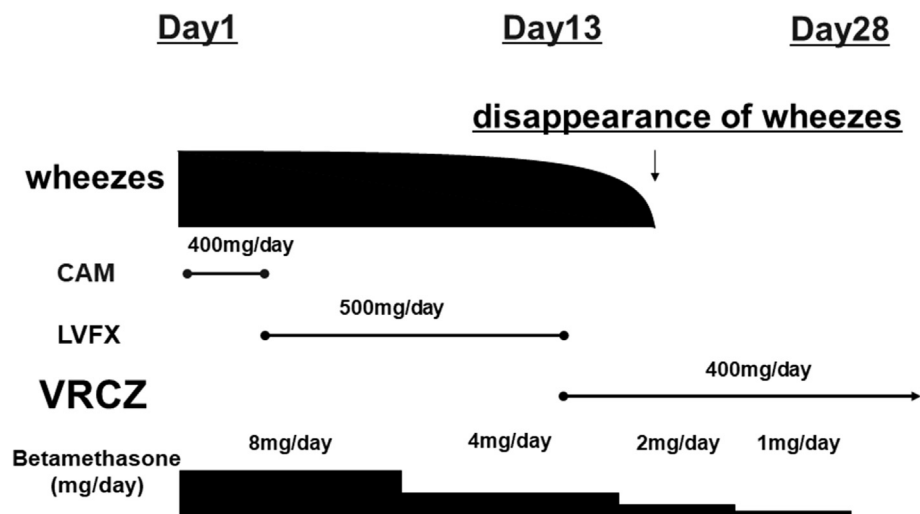


Fig. 2. Clinical course. CAM, clarithromycin; LVFX, levofloxacin; VRCZ, voriconazole.

VRCZ was similarly reported to upregulate several chemokines, including interferon- γ (IFN- γ).⁵ Furthermore, ITCZ increases the serum level of glucocorticoids.⁶ Azoles are expected to improve asthma control in SAFS, not only by their direct killing effects but also through immunologic effects and increased corticosteroid bioavailability.

Some clinical reports have described the efficacy of long-term antifungal therapy for SAFS in the maintenance phase. Clinical trials of ITCZ in patients with SAFS (FAST study) have shown that ITCZ improves the Asthma Quality of Life Questionnaire (AQLQ) score and morning peak flow and reduces the serum IgE level.² However, in clinical trials of VRCZ for SAFS (EVITA 3 study), there were no

significant differences in the total number of severe exacerbations or the AQLQ score between the VRCZ and placebo group.⁷ It is not clear why the EVITA 3 study demonstrated no benefit on asthma control; however, this finding may be due to the duration of VRCZ treatment being shorter than that of ITCZ (12 vs. 32 weeks). Furthermore, the pharmacokinetic effect of ITCZ on corticosteroid bioavailability might have influenced the differences in these two clinical trials.

We choose VRCZ for therapy, given its potent efficacy in reducing the fungal burden. Indeed, VRCZ was reported to show lower MICs against clinical isolates of *A. fumigatus* *in vitro* than ITCZ.⁸ With regard to the treatment of SAFS, the direct killing effect

is thought to be more important than the immunologic effect or increased corticosteroid bioavailability when a high fungal burden is expected. The presence of a high fungal burden might be a clinical feature of patients who are likely to respond to antifungal therapy.

There remains a small possibility that the patient's respiratory symptoms, including wheezing, were caused by *aspergillus* bronchitis rather than an exacerbation of SAFS. We think that the symptoms were mainly caused by asthma because the patient showed typical features of asthma, such as wheezing which fluctuated during the day and became worse at nights. The typical features of asthma could not be explained by *Aspergillus* bronchitis. Moreover, the current case is not a typical case of SAFS. Although serum *Aspergillus* IgG antibody is usually negative in patients with SAFS, it was positive in the current case. However, serum *Aspergillus* IgG antibody was reported to be positive in *Aspergillus* bronchitis.⁹ Furthermore, with the exception of the *Aspergillus* IgG antibody, the clinical features were consistent with SAFS, and the patient did not meet any of the currently available diagnostic criteria for ABPA. Thus, we think that it was reasonable to diagnose SAFS complicated with *Aspergillus* bronchitis.

This is the first report of an exacerbation of asthma in a SAFS patient complicated with *Aspergillus* bronchitis that was successfully treated with VRCZ. Physicians should consider the possibility of chronic *Aspergillus* infection of the lower airways and addition of antifungal therapy if necessary, when encountering a patient with SAFS whose exacerbation is unresponsive to SCSs.

Conflict of interest

The authors have no conflict of interest to declare.

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