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CASE REPORT

Improvement of Mucoid Impaction with Dupilumab in a Severe Asthma Patient

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ABSTRACT

Different from intrabronchial mucus accumulation in bronchiectasis caused by chronic inflammation, mucoid impactions are observed in patients with allergic bronchopulmonary aspergillosis (ABPA) and bronchial asthma. A 62-year-old man was referred to our hospital for treatment of bronchial asthma. Five years ago, he had a coronary stent insertion for myocardial infarction and was diagnosed with bronchial asthma. The stent was suspected to be related to the onset of asthma. Inhaled corticosteroid/long-acting beta agonist was not sufficient to control the condition. He received dupilumab, a humanized anti-human IL-4/13 receptor monoclonal antibody (biologic therapy). Bronchial mucoid impactions disappeared by single administration of the biologic therapy and there has been no recurrence of mucoid impactions for over a year. Although very rare, we do believe that information regarding asthma phenotype in this patient, indication and administration method for dupilumab, and changes before and after administration of dupilumab will provide some suggestive information on treatment for patients with a similar course in the future.

Keywords: mucoid impaction, bronchial asthma, dupilumab, anti-interleukin-4 receptor α monoclonal antibody, biologics.

INTRODUCTION

Allergic bronchopulmonary mycosis (ABPM) is a chronic inflammatory disease caused by fungi that induce allergic reactions in the respiratory tract (1) Among fungi associated with ABPM, *Aspergillus fumigatus* is the most common, and if a relationship with *Aspergillus fumigatus* is found, allergic bronchopulmonary aspergillosis (ABPA) is diagnosed (1). In the diagnosis of ABPA, central bronchiectasis and mucoid impactions are characteristic in chest imaging (2). Chronic inflammation and impaired clearing mechanism in patients with bronchiectasis leads to intrabronchial retention of plugs of mucus. On the other hand, bronchial mucoid impactions can be observed in some patients with bronchial asthma who do not meet the diagnostic criteria for ABPA (3-5). In re-

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cent years, progress has been made in elucidating the pathology of bronchial asthma, and antibody drugs, biologics that control the involved cytokines have been brought into clinical practice and are now being used to treat patients with severe uncontrolled asthma (6). Furthermore, some cases have been reported in which bronchial mucoid impactions were improved by administration of such biologics (7-10).

We recently treated a patient with bronchial asthma presumed to be inflammation predominant asthma (cluster 5) in the classification by Haldar *et al* (11) and cluster 5 in the classification by Moore *et al* (12) using a biologic, dupilumab, a humanized anti-human IL-4/13 receptor monoclonal antibody (6). In this patient, we achieved control not only of bronchial asthma symptoms but also of the mucoid impactions in the central bronchus. Although our patient did not match ABPA diagnostic criteria (1), we do believe his clinical course would provide some suggestive information on treatment for patients with a similar course in the future. ❑

CASE REPORT

A 62-year-old man was referred to our hospital because of poorly controlled bronchial asthma. Five years ago, he had a coronary stent placed for the treatment of acute myocardial infarction. The patient developed bronchial asthma five years ago and since then, he has been regularly using inhaled corticosteroids/long-acting β2 agonist (ICS/LABA, budesonide, formoterol fumarate hydrate) inhaler. Around the same time, nasal polyps were pointed out, and they were histologically diagnosed as eosinophilic sinusitis. The serum non-specific IgE level was 212 (normal range: up to173) IU/mL and the specific antibody titer against *Aspergillus* was less than 0.10 IU/mL. No other specific IgE was detected. Two years ago, he developed anaphylactic shock to analgesics and was taken to an ambulance for treatment and hospitalized for a week. Cough, sputum, nocturnal wheezing and dyspnea persisted for several months despite high-dose ICS/LABA and antiallergic medications. Asthma has worsened two to three times a year, but systemic steroids were not administered because the patient did not wish to receive them. On admission, he had wheezing and prolongation of exhalation. A chest computed tomography (CT) scan revealed bilateral bronchiectasis and mucoid impactions (Figure 1). Blood tests showed WBC 12000/μL (eosinophils 6.7%) and C-reactive protein (CRP) 0.12 mg/dL. Pulmonary function test showed FVC 2.40 L, FEV_1 1.38 L (% FEV_1 42.4%), FEV_1 (G) 69.4%, PEF 53.1%, V50 0.71 L/sec (17.0%). He was diagnosed with severe bronchial asthma and was given a subcutaneous injection of 600 mg dupilumab. Symptoms continued to improve within two weeks of administration. The patient was satisfied with that good response and did not want to receive any additional dupilumab, although he continued ICS/LABA inhalation thereafter. There was no exacerbation of symptoms. A chest CT taken 1.5 years after administration of dupilumab also showed no development of mucoid impactions, although bronchiectasis remained (Figure 2). ❑

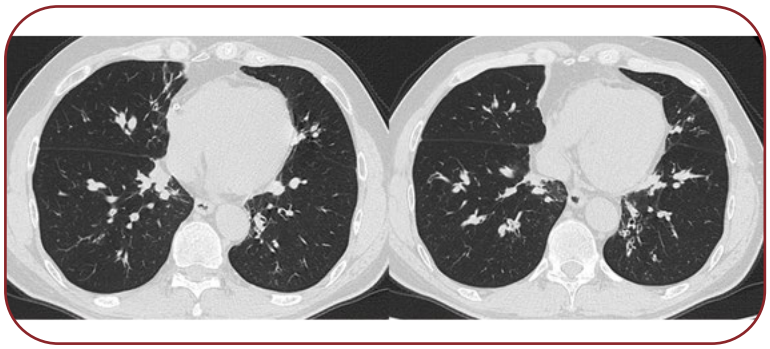

FIGURE 1. Chest CT scan taken on admission revealed bilateral bronchiectasis and mucoid impactions

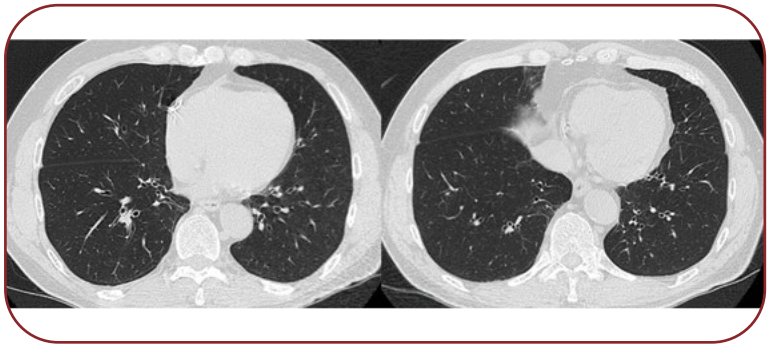

FIGURE 2. Chest CT taken 1.5 years after administration of dupilumab also showing disappearance of mucoid impactions, although bronchiectasis remained

DISCUSSION

Phenotype of asthma in this patient was considered to be inflammation predominant asthma (cluster 5) in the classification by Haldar

et al (11) and cluster 5 in the classification by Moore *et al* (12). Before administration of dupilumab, clinical symptoms were poorly controlled even with high doses of ICS/LABA inhalation, and the results of respiratory function tests also reflected the clinical status. Therefore, it was determined that dupilumab was indicated. After starting dupilumab, clinical improvement was maintained with treatment using the usual dosing regimen.

Mucoid impactions are characteristic findings in ABPA or ABPM patients (1, 2). It is known that the majority of patients with ABPA have comorbid bronchial asthma (1). Mucoid impactions are also found in patients with bronchial asthma (3-5), as observed in our patient. Although ABPA was not diagnosed in these patients, there might have been an allergic mechanism similar to ABPA. Several biologics are currently available for severe bronchial asthma. Among them, mepolizumab and dupilumab were administered to ABPA and bronchial asthma patients with mucoid impactions (6-10). Mepolizumab is a monoclonal antibody against IL5. Dupilumab is a fully human anti- IL-4 receptor α (IL-4Rα) monoclonal antibody that blocks both IL-4 and IL-13 signaling because IL-4Rα is a common subunit of IL-13 and IL-4 (11). As far as we could search the literature, there were five reports on the administration of these biologics to patients with mucoid impaction (6-10). Four of the five reports showed improvement in mucoid impactions by these biologics (7-10). Only one report, however, described massive atelectasis by mucoid impaction in an asthma patient during treatment with anti-IL-5 receptor antibody (6). In patients who responded to biologics, the duration of administration was 1-20 months (7-10). A case of particular interest was described by Terashima *et al*, who reported that the disappearance of mucoid impaction was confirmed after a single mepolizumab, a humanized monoclonal antibody directed at IL-5 treatment; however, their findings did not show any long-term image changes (10). Kai *et al* reported a successful management of recurrent ABPA after switching from mepolizumab to dupilumab (7). Compared with the course of these patients, the following two points were noted in the clinical course of our patient: 1) mucoid impaction disappeared after a single dose of dupilumab; and 2) there was no recurrence of mucoid impaction for a long period of time. Should we assume that production of mucoid impaction was continuously suppressed because the usual dosing regimen of dupilumab was administered once every two weeks? Although the mechanism was unknown, the course was considered to be noteworthy. It is known that these biologics suppress secretion into the respiratory tract (6). However, it is not clear how mucoid impactions that have been produced and accumulated in the airways disappears, and how the disappearance of mucoid impaction is maintained. It is speculated that by suppressing secretion, the phagocytic ability of macrophages catches up, while mucoid impaction becomes easier to expectorate, resulting in the disappearance of mucoid impaction, and that such a mechanism would be maintained by continuous administration of dupilumab. Another interesting point in the clinical course of this patient was that bronchial asthma, eosinophilic sinusitis and anaphylactic shock developed almost at the same time several years after acute myocardial infarction and stent placement. In this patient, blood eosinophils were less than 5% before stent implantation, but after implantation, they remained above 5% until administration of dupilumab. Faybusovich *et al* described a patient who developed a generalized skin allergy several weeks after placement of sirolimus-eluting 36L stent (14). Although no asthma episodes have been reported in this stented patient, a patch test showed a reaction to nickel/cobalt in the stent material (14). On the other hand, Gupte *et al* described a patient with sirolimus-related pulmonary toxicity mimicking 'asthma like' symptoms (15). Although very rare, some patients might experience an allergic reaction after coronary stent insertion. If so, as physicians, we need to be careful.

We described a patient whose mucoid impactions were resolved with a single administration of dupilumab, followed by a long period without relapses. The clinical course of this patient might have implications for the treatment of future patients with a similar course. ❑

CONCLUSIONS

Some patients with severe bronchial asthma have mucoid impaction which might be controlled using biologics. Therefore, biologics could be a treatment option for these patients. ❑

Statement of ethics: This study was approved by the institutional ethics committee of our institute (NO 2325). Written comprehensive informed consent at the time of admission for obtaining pathological specimens was obtained from the patient.

Conflicts of interest: none declared.

Financial support: none declared.

Authors' contributions: SH and HS designed the study. SH, SO, TI, EO and HS collected the data. SS and HS prepared the manuscript. All Authors approved the final version for submission.

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