Annals of Otolaryngology Head and Neck Surgery
Case Report (ISSN 2835-7132)

A Case Report of Refractory AFRS That Appears to Have Been Successful with Benralizumab

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Citation: Akira Yorozu, Kizuku Owada, Fumie Ito, Ryoto Yajima, Takuya Kakuki, Ryo Miyata, et al. A Case Report of Refractory AFRS That Appears to Have Been Successful with Benralizumab. *Annal of Otol Head and Neck Surg. 2024;3(5):1-7.*

Received Date: 08 November, 2024; **Accepted Date:** 11 November, 2024; **Published Date:** 12 November, 2024

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ABSTRACT

Allergic fungal rhinosinusitis (AFRS) is a chronic sinusitis characterized by type I and III allergic reactions to non-invasive fungi, resulting in the production of eosinophilic mucus. Here, we report a successful use of biologics in a patient with refractory AFRS who underwent multiple endoscopic sinus surgeries (ESSs), discussing our experience. The patient, a 45-year-old man with a history of bronchial asthma and dairy farming work, underwent the first ESS for bilateral chronic sinusitis in 2004. Although nasal sinus symptoms stabilized after the initial surgery, recurrent sinusitis let to six ESS procedures since 2012. Alongside surgical interventions, conservative treatments, including drug therapies and nasal cavity rising, improved nasal congestion and discharge but left residual right eye pain. In February 2020, benralizumab was initiated for asthma treatment in the pulmonary medicine department, leading to significant improvement in the right eye pain. Three years post-treatment commencement, no recurring symptoms have been observed. As AFRS is rare, treatment guidelines are yet to be established. Although biologics for chronic rhinosinusitis with nasal polyp have gained attention, biologics for AFRS have limit reported cases. This report suggests that anti-IL-5 receptor antibodies are effective against AFRS; however, their precise mechanism remains unclear. Further investigations into the pathogenesis of AFRS and the application of biological agents are warranted.

INTRODUCTION

Allergic fungal rhinosinusitis (AFRS) emerged as a new disease concept first reported in 1983 1), with diagnostic criteria proposed by Bent and Kuhn in 1994 2). AFRS presents as a recurrent rhinosinusitis classified as sinus mycosis caused by Aspergillus, characterized by type I and III allergic reactions upon fungal exposure. Its diagnosis relies widely on the criteria established by the American Academy of Allergy, Asthma, and Immunology

3). Prevalence varies based on climate and other factors, notably being higher in hot and humid regions. However, in Japan, it is reported to be 3.9% or 8.3%.

Common treatments involve surgical interventions and drug therapies, including systemic steroids. Despite multimodal treatments, the disease frequently resists therapy and recurs. Recent considerations position AFRS as a type 2 inflammatory disease sharing an endotype with eosinophilic sinusitis (ECRS). Biologics targeting type 2 inflammation for AFRS have been reported to be effective. Particularly, some reports on the use of Dupilumab, an IL-4/13 receptor inhibitor, have suggested successful outcomes 7)-9). However, results from clinical trials with a large number of patients have not been reported. Allergic bronchopulmonary aspergillosis (ABPA), a type I hypersensitivity to aspergillus, was first described by Hinson et al. in 195210). Considering the resemblance clinical features between ABPA and AFRS, the latter is seen as the upper respiratory tract manifestation of ABPA. However, insufficient case reports linking AFRS with ABPA limit the establishment of its treatment protocols. In this paper, we present our long-term follow-up experience with the AFRS associated with ABPA. We discuss a case of refractory AFRS that showed no improvement following multiple surgeries but experienced resolution soon after benralizmab administration-an IL-5R inhibitor. Furthermore, we explore the efficacy of benralizmab in this context.

CASE PRESENTATION

We present the case of a man in his 40s with recurrent rhinosinusitis. The chief complaints were recurrent purulent rhinorrhea, nasal obstruction, and right eye pain. In 2004, the patient underwent bilateral endoscopic sinus surgery (ESS) for chronic sinusitis. The patient had a history of bronchial asthma and eosinophilic pneumonia, and was engaged in dairy farming.

In 2010, patient eosinophilic pneumonia worsened and was treated with systemic steroids. Pathological histology of the lung biopsy showed mucous plugs with Charcot-Leyden crystals and macrophage/eosinophil infiltration into the alveoli (Figure 1A, B). An increase in specific antibody titers to fungi, including Aspergillus, led to a diagnosis of ABPA (Figure 1C). In 2012, the patient developed headache and purulent rhinorrhea. Soft tissue shadows were observed on both sides of the sphenoid sinuses on CT images (Figure 2A). Therefore, bilateral ESS was performed twice in 2013. Post-surgery, although his nasal sinus symptoms improved, his eosinophilic pneumonia worsened again, requiring systemic steroids. In 2014, 2 years after the second surgery, purulent rhinorrhea (Figure 2B) and right eye pain recurred, and soft tissue shadows were observed in the right ethmoid sinus. Therefore, a third ESS was performed. Histopathological examination confirmed the presence of aspergillus and eosinophilic mucin, leading to AFRS diagnosis (Figure 2C). Despite continuous nasal rinsing and local steroid therapy, the symptoms recurred repeatedly and necessitated three ESS procedures. However, the right eye pain did not subside. Retrospectively focusing on the soft tissue shadows in the CT images, the high absorption area on the left side moved to the right side in 2013, consistent with the chief complaint of pain in the right eye. The right sphenoid sinus was narrowed by bone thickening of the sinus wall. However, no increase in the soft tissue shadow was observed. Serum T-IgE levels were elevated, consistent with worsened eosinophilic pneumonia and nasal sinus symptoms.

In 2020, although his respiratory symptoms were stable, benralizumab was initiated in the Department of Respiratory Medicine. Soon after benralizumab administration, his sinus symptoms improved markedly, and the

nasal findings have remained good for 3 years. No change was observed in the CT findings, and both serum T-IgE and eosinophil counts in the peripheral blood decreased 2 years after benralizumab administration (Figure 3).

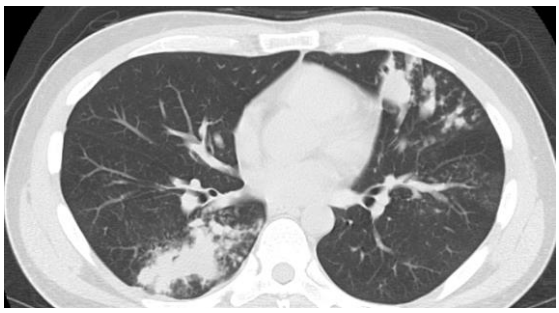


Figure 1A: Computed tomography scans of the patient's chest of ABPA.

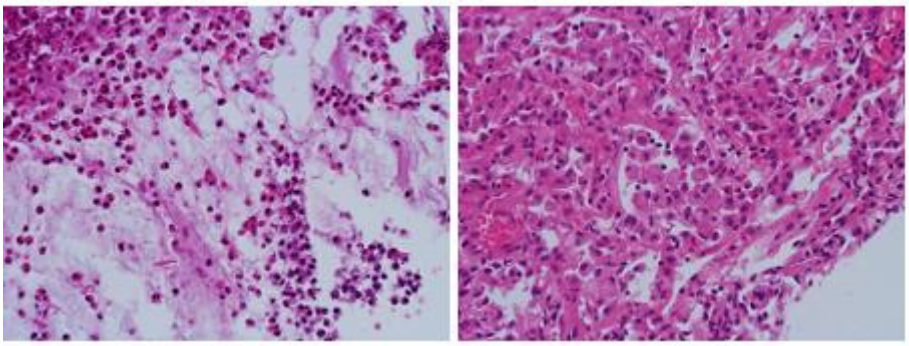


Figure 1B: Transbronchial Lung Biopsy (TBLB) indicated Mucus plug with Charcot-Leyden crystals (left) and macrophage and eosinophil infiltration into the alveoli (right).

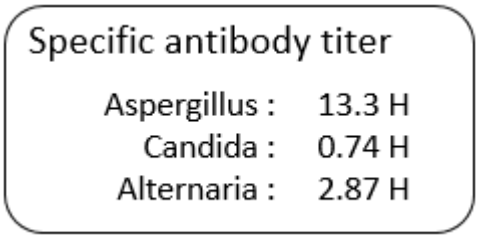


Figure 1C: High specific antibody titer against fungi.

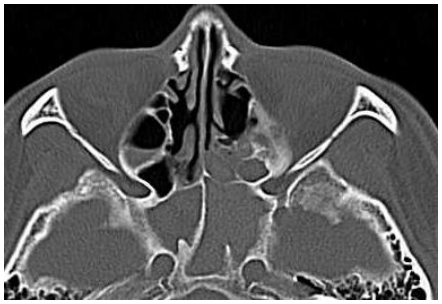


Figure 2A: Computed tomography scans of the patient's nasal sinuses.

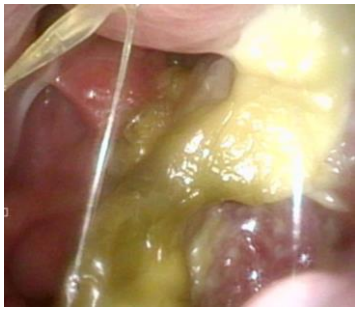


Figure 2B: Endoscopic findings of the nasal cavity in a patient with Allergic fungal rhinosinusitis (AFRS).

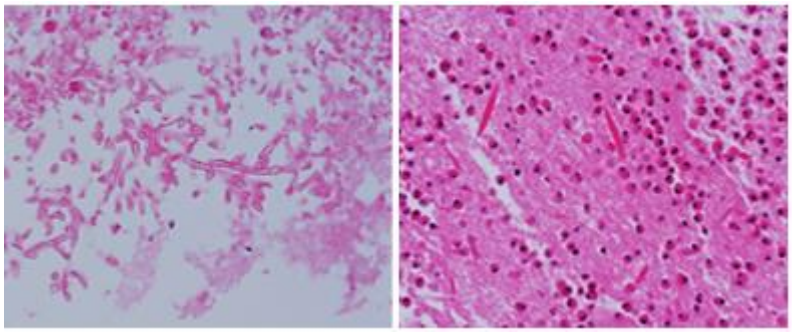
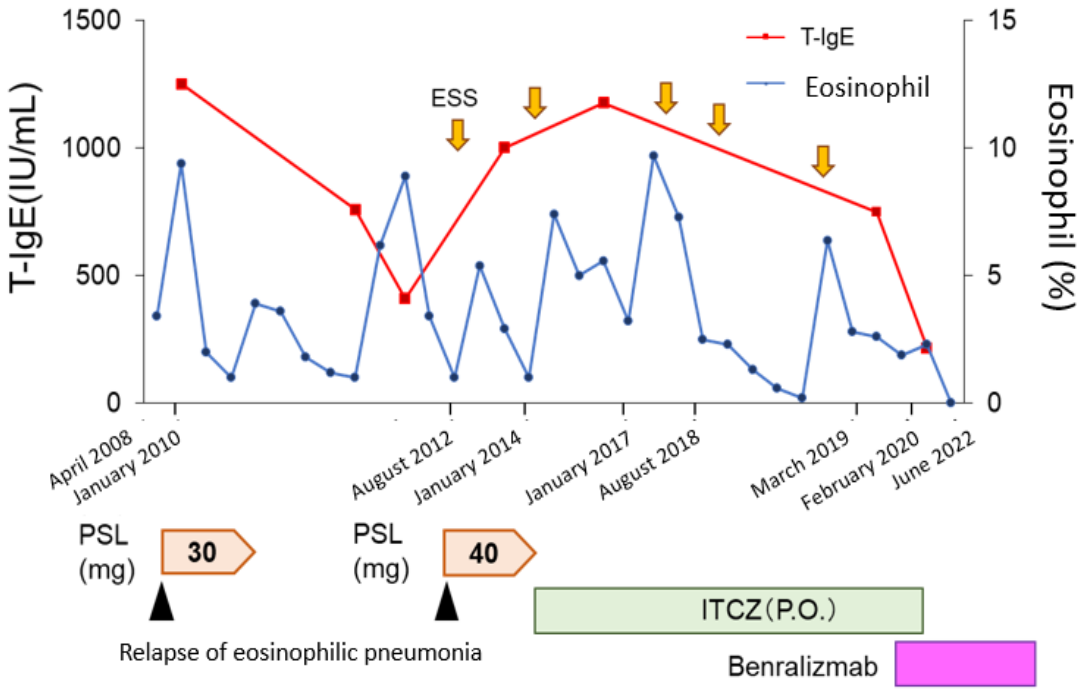


Figure 2C: Histopathological examination confirmed the presence of aspergillus （left） and eosinophilic mucin (right), leading to AFRS diagnosis.



PSL: Prednisolone; ITCZ: Itraconazole

Figure 3: Treatment course of this case

DISCUSSION

AFRS is classified as a fungal sinusitis due to its etiology and is also categorized as chronic rhinosinusitis with nasal polyp based on its clinical findings of nasal polyps and sinusitis. Recent studies have suggested that AFRS is a type 2 inflammatory disease triggered by type 2 cytokines (IL-4, IL-5, and IL-13) induced by fungi, sharing an endotype similar to that of ECRS6). AFRS and ECRS are often treated similarly due to their comparable clinical and pathological characteristics, including eosinophil infiltration in nasal polyps and eosinophil count in peripheral blood. We conducted a study involving 55 patients who underwent surgery for bilateral chronic sinusitis in the last 5 years at our institution. Among them, 21 (38.2%) were diagnoses with ECRS, 3 (5.5%) with chronic non-invasive mycosis, 1 (1.8%) with AFRS, and 2 (3.6%) met the diagnostic criteria for both ECRS and AFRS. These findings indicate that approximately 10% of ECRS cases may potentially involve AFRS. Although AFRS is often localized in hot and humid regions, this case was reported from the Tokachi region in Hokkaido, characterized by lower average temperature and humidity than those in previously reported regions in Japan12), 13). The patient, a dairy farmer, suggests that occupational exposure to fungi and patient personal allergy profile were significant factors in this case14).

Unlike ECRS, AFRS frequently presents as a unilateral lesion, and eosinophilic mucin may be localized unilaterally or even in bilateral lesions. Eosinophilic mucin manifests as a high absorption area in soft tissue conditions on CT images, prompting consideration of this disease in cases of asymmetric soft tissue shadows in bilateral sinusitis5)12). In the present case, the patient initially had bilateral sinusitis, but the high absorption area on the CT images was confined to the left side. The postoperative recurrence was confined to the sphenoid sinus on the right side and resulted in recurrence on the opposite side15). AFRS with unilateral bone destruction has been reported12), 16-18) and may need to be differentiated from invasive fungal sinusitis or malignancies. However, no significant bone destruction was confirmed during the course of the disease. AFRS is characterized by high IgE levels compared with eosinophil count. In the present case, IgE levels were particularly high during the period when ABPA worsened or the nasal sinus symptoms recurred. However, the efficacy of oral antifungal therapy for AFRS has not been established19). Although oral administration of antifungal agents was continued for ABPA treatment, recurrent pain in the right eye, a symptom of AFRS, suggested that oral administration of antifungal agents was ineffective.

Recently, the efficacy of dupilumab, a biological agent targeting IL-4/13, was demonstrated for recurrent ECRS treatment and is now widely used. The response to biologics targeting type 2 inflammation is also anticipated in AFRS, which is considered to share an endotype with ECRS. Benralizumab is an afucosylated monoclonal antibody that targets and binds to the IL-5 receptor and has ADCC activity that induces the apoptosis of eosinophils and eliminates eosinophils in the peripheral blood and tissues. Benralizumab has been approved for asthma treatment and is particularly effective in patients with high eosinophil counts19). Although marked reductions have been reported in both eosinophil counts and IgE levels after treatment with benralizumab in patients with ABPA asthma19), no cases of AFRS treatment with benralizumab for AFRS has been previously reported21)22). The small number of reports regarding cases with AFRS combined with ABPA has been attributed to the potential oversight of their coexistence, despite sharing a common pathology, due to their treatment in

separate departments9). The standard treatment for AFRS typically involves ESS, local/systemic steroid administration, and local antifungal therapy. Recently, the effectiveness of dupilumab, a biological agent, has been demonstrated. Our experience with this case suggests that benralizumab could potentially serve as another treatment option.

CONCLUSION

Here, we present a case of refractory AFRS treated with benralizumab for respiratory disease. AFRS, a type 2 inflammatory disease, lacks comprehensive understanding due to its limited case studies. Moreover, patients often exhibit resistance to conventional therapies, warranting future investigations into the efficacy of biologics. This particular case demonstrated a distinct clinical trajectory with complications of ABPA and relatively gradual disease progression, inviting anticipation for further insights.

FUNDING INFORMATION: "This study was supported in part by JSPS KAKENHI Grant Number 24K12676 (A. Yorozu)."

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