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A case of eosinophilic granulomatosis with polyangiitis showing multiple white lichen lesions on the airway mucosa

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ABSTRACT

A 70-year-old man, treated for asthma for 2 years and chronic sinusitis for several months, presented with fever, numbness in the lower limbs, heaviness in the head, gross hematuria, and black stools. He also had eosinophilia, elevated serum IgG4 levels, high levels of myeloperoxidase-anti-neutrophil cytoplasmic antibodies (MPO-ANCA), and pulmonary infiltrative shadows. Bronchoscopy revealed multiple white flattened lesions (white moss) on the airway mucosa, suggesting mycobacterial infection or malignancy. A biopsy from tracheal mucosa revealed airway inflammation with marked eosinophil infiltration. The patient was diagnosed with eosinophilic granulomatosis with polyangiitis (EGPA) and treated with steroids, and all findings improved. However, a year and a half after the initiation of treatment, eosinophils and IgE gradually increased; subjective symptoms, such as asthma symptoms and numbness in the lower limbs, worsened; and ANCA, which had been negative, turned positive. Therefore, we suspected disease relapse and anti-IL-5 antibody (mepolizumab) treatment was initiated. Thereafter, ANCA turned negative again, eosinophils and IgE normalized, and subjective symptoms decreased. The presence of airway mucosal lesions in EGPA is relatively rare, and we report this case as a valuable case owing to the interesting bronchoscopic findings that are worth comprehending as a respiratory physician.

1. Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA) is associated with bronchial asthma and allergic rhinitis as preceding symptoms, followed by systemic vasculitis and extravascular granulomatosis mainly in small and medium-sized blood vessels through eosinophilia and eosinophil infiltration of organs, resulting in various clinical symptoms such as fever, weight loss, polyneuritis mononeuritis, and purpura. Approximately 40% of cases are positive for ANCA [1], and it is regarded as one of the ANCA-related vasculitis. It is most common in women between the ages of 30 and 60 years. According to the 2010 Survey and Research Group on Refractory Vasculitis, the number of new patients in Japan is approximately 100 annually, and the number of patients visiting medical facilities annually is approximately 1,800. According to Martin et al. [2], the incidence of EGPA in the general population is about 6.8 cases per million people; however, the incidence is as high as 64.4 cases per million people in patients with asthma.

Cottin et al. reported that the respiratory symptoms of EGPA are variable [3]. In this report, bronchoscopy was performed in 92 cases and demonstrated diffuse inflammation of the bronchial mucosa in 27 (29%) patients, mucous secretions in 14 (15%) patients, and whitish granulations in eight (9%) patients. In the present study, we report a case of EGPA with multiple white lichen lesions in the airway mucosa. It is relatively rare to find tracheobronchial mucosal lesions in EGPA, and we report this case with a review of the literature.

2. Case report

A 70-year-old man, treated for asthma for 2 years and chronic sinusitis for several months developed fever, numbness in the lower

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limbs, heaviness in the head, gross hematuria, and black stools. He visited the urology department and underwent cystoscopy and ureteroscopy; however, no abnormal findings were detected. Following this, weight loss and decreased appetite also appeared, and the patient visited a local doctor and received medical treatment, without improvement. The numbness worsened and spread to the left palm. The patient was referred to our department and was admitted for further investigation and treatment.

On admission, physical examination revealed no abnormalities on auscultation and numbness in the left fifth finger, the ulnar one-third of the palm, and the left and right soles. Laboratory findings on admission were: white blood cell count, 16.2 × 10^3/μL; eosinophils, 50.3% (8178 cells/μL); hemoglobin, 12.4 g/dL; platelets, 330 × 10^3/μL; total protein, 7.2 g/dL; serum albumin, 3.0 g/dL; serum urea nitrogen, 15.8 mg/dL; serum creatinine, 1.02 mg/dL; serum uric acid, 2.9 mg/dL; IgG, 1814 mg/dL; IgA, 101 mg/dL; IgM, 149 mg/dL; IgE, 1846 IU/L; and C-reactive protein, 6.67 mg/dL. On serologic examination, his MPO-ANCA was elevated at 425 EU (normal <3.4 EU), proteinase 3-ANCA (PR3-ANCA) was negative at less than 1.9 EU. Anti-DNA antibody, anti-nuclear antibody, and anti-glomerular basement membrane antibody were not detected. Complement values were normal. Urine qualitative analysis showed urine protein (2+), urine protein quantitative 100 mg/dl, urine glucose (−), urine occult blood (2+), urine sediment showed red blood cell count 30–49/HPF, white blood cell count 5–9/HPF. Creatinine clearance (Cockcroft-Gault equation) was 50 ml/min. Chest radiographs revealed an irregularly demarcated infiltrative shadow in the right middle lung field with peripheral predominance, and chest computed tomography demonstrated a ground-glass opacity and infiltrative shadow in the right lung with the upper lobe predominance (Fig. 1).

The clinical course is illustrated in Fig. 2. After admission, magnetic resonance imaging of the head and spine was performed; however, no compressive lesion causing numbness was detected. The neurotransmission test revealed a decrease in the compound muscle action potential of the left tibial nerve. The fecal occult blood reaction was positive; however, upper and lower gastrointestinal endoscopy revealed no evidence of gastrointestinal bleeding or other possible causes. Electrocardiography and echocardiography also showed no significant findings. Bronchoscopy revealed multiple white flattened lesions (white moss) on the airway mucosa, suggesting mycobacterial infection or malignancy (Fig. 3). A biopsy from tracheal mucosa revealed airway inflammation with marked eosinophil infiltration, although there were no findings suggestive of granuloma or vasculitis. Bronchoalveolar lavage showed an increase in total cell count and eosinophil fraction, suggesting a lesion similar to chronic eosinophilic pneumonia. In contrast, transbronchial lung biopsy showed minimal eosinophilic infiltration and no evidence of granuloma or vasculitis. Additional immunostaining revealed an IgG4/IgG positive cell ratio of 98% and infiltration of IgG4 positive cells (Fig. 4). Bronchial asthma, eosinophilia, and vasculitis symptoms, such as fever, weight loss, and polyneuritis, were observed. We started steroid treatment under the diagnosis of EGPA. Steroid pulse therapy was administered for the first 3 days, and then oral prednisolone 50 mg/day (about 1 mg/kg/day) was initiated and gradually reduced. Thereafter, fever rapidly improved, and subjective symptoms such as head heaviness disappeared. After the initiation of treatment, hematuria and black stools were not observed, and numbness, although still slightly present, was reduced. The eosinophil and white blood cell counts improved markedly after the steroid pulse and normalized, and the IgE and MPO-ANCA count decreased and then normalized. One month after the start of treatment, the patient underwent a repeat bronchoscopy and chest imaging, and the pulmonary lesions and bronchoscopic findings observed at the time of admission were markedly improved. The prednisolone dose was reduced to 30 mg/day, and the patient was discharged on the 72nd day. Thereafter, the dose of prednisolone (PSL) was gradually tapered into 5–7.5mg/day; however, eosinophil and IgE levels steadily increased, ANCA became positive, and subjective symptoms, such as asthma and numbness in the lower limbs, worsened after 1.5 years of treatment. We thought it was a relapse and considered concomitant use of immunosuppressive drugs, but could not obtain consent due to concerns about side effects. The mode of recurrence was mainly worsening of asthma symptoms, elevated peripheral blood eosinophil count, and MPO-ANCA positivity. Since there was no worsening of vasculitis and no appearance of serious organ lesions, we decided to select mepolizumab. ANCA, which had been positive, turned negative again, eosinophils and IgE normalized again, and subjective symptoms decreased. The patient's condition remained stable using steroids and mepolizumab.

3. Discussion

EGPA is a disease that combines allergic diseases such as bronchial asthma, hypereosinophilia, eosinophilic infiltration of the blood vessel wall, and extravascular granuloma. It was formerly known as Churg-Strauss syndrome (CSS) or allergic granulomatous angiitis (AGA). This disease was proposed as an independent disease from periarteritis

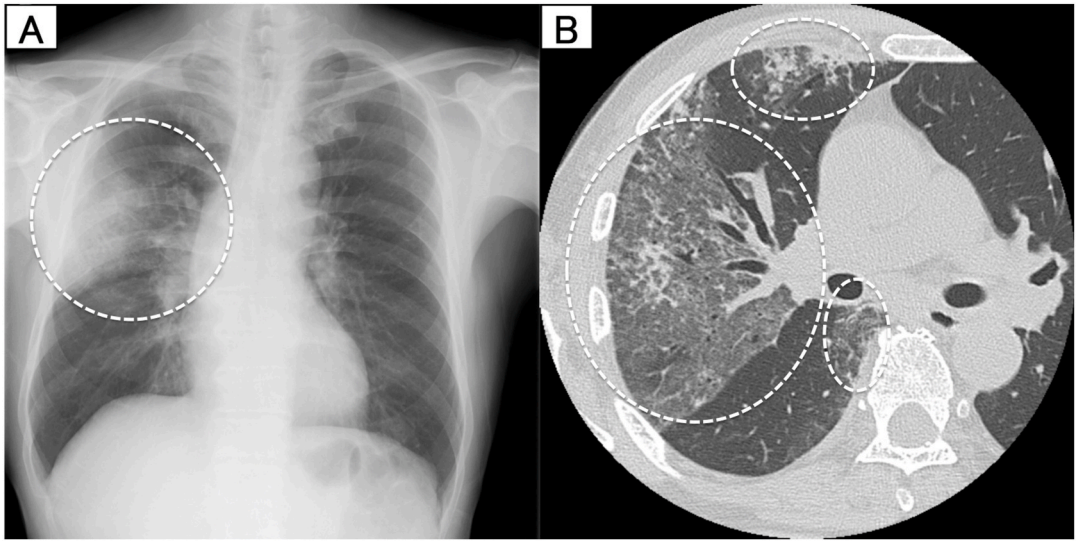

Fig. 1. Chest radiographs(panel A) showed an irregularly demarcated infiltrative shadow in the right middle lung field with peripheral predominance, and chest computed tomography(panel B) showed a ground glass opacity and infiltrative shadow in the right lung with upper lobe predominance.

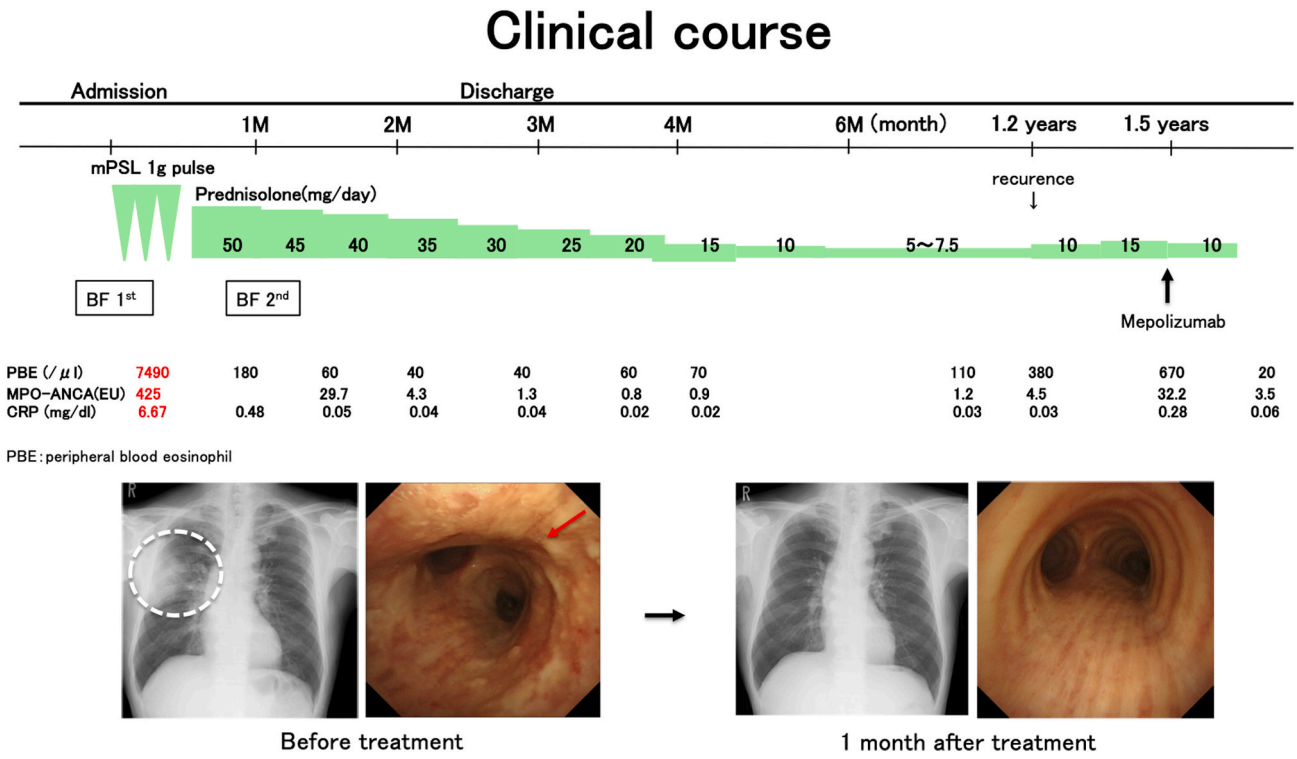

Fig. 2. With steroid treatment, clinical symptoms, peripheral blood eosinophil count, CRP, and serum IgE decreased, and MPO-ANCA became negative. Lung abnormal shadows and bronchoscopic findings also improved quickly 1 month after treatment. One and a half years after the start of treatment, signs of relapse were observed, and anti-IL-5 antibody (Mepolizumab) was added.
PBE: peripheral blood eosinophil.

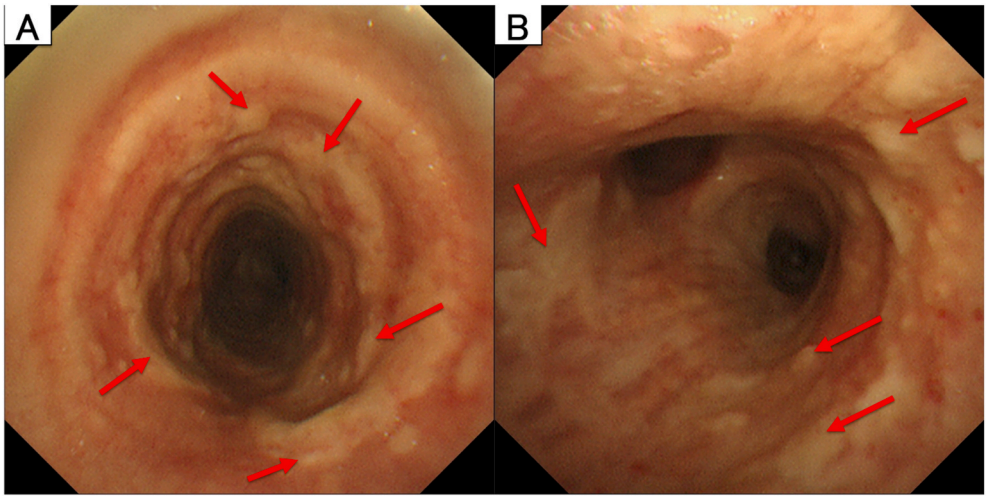

Fig. 3. Bronchoscopy revealed multiple white flattened lesions (white moss) on the airway mucosa (panel A, B). A biopsy from the tracheal mucosa revealed airway inflammation with marked eosinophil infiltration.

nodosa by the United States pathologists Churg and Strauss in 1951 [4]. At the 2012 Chapel Hill Conference, CSS was renamed EGPA, and simultaneously the name of the disease was changed by the research group of the Ministry of Health, Labor and Welfare (MHLW) of Japan [5].

EGPA was diagnosed using the classification criteria of the American College of Rheumatology (ACR) in 1990 [6] and the Japanese criteria of the MHLW [7]. (see Table 1) The ACR criteria included (1) bronchial asthma; (2) increased peripheral blood eosinophils; (3) mononeuritis, polyneuritis, or polyneuritis; (4) pulmonary infiltration; (5) sinus abnormalities; and (6) eosinophilic infiltration of extravascular tissues. In this case, all six items were present and a diagnosis of EGPA was established. In contrast, according to the Japanese diagnostic criteria, AGA is diagnosed when histological findings, such as granulomatous or fibrinoid necrotizing vasculitis or extravascular granuloma of the smallest blood vessel, are met, and CSS (currently EGPA) is diagnosed when no histological findings are obtained and the diagnosis is based on clinical symptoms. In this case, bronchial asthma, eosinophilia, fever, weight loss, and polyneuritis were observed among the major clinical findings. Although the major histological findings were not observed, since the patient had bronchial asthma for 2 years and the three major clinical items were present, this patient could be also diagnosed as EGPA

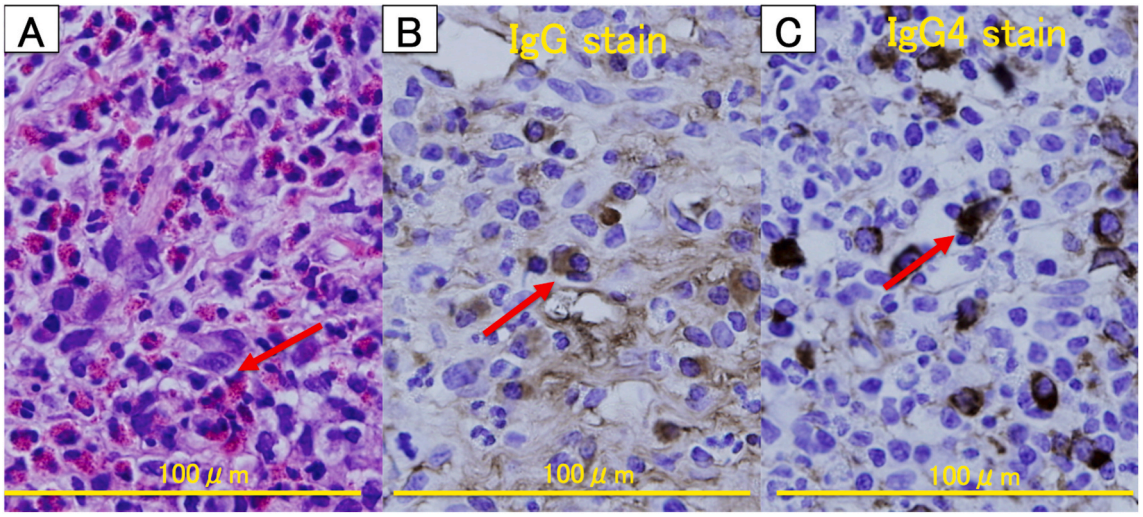

Fig. 4. Biopsy of the tracheal mucosa revealed a marked infiltration of eosinophils(panel A). Additional immunostaining showed an IgG4(panel C)/IgG(panel B) positive cell ratio of 98% and infiltration of IgG4 positive cells.

Table 1
Comparison of ACR criteria with Japanese criteria.

＜Japanese Criteria＞
Diagnostic Criteria for Allergic Granulomatous Angiitis (Churg–Strauss Syndrome)
Definition
Criteria for diagnosis
1) Major clinical findings
(1) Bronchial asthma or allergic rhinitis
(2) Eosinophilia
(3) Signs/symptoms of vasculitis: Fever ＞38℃ for ＞ 2 weeks), weight loss (>−6 kg in <− 6 months), mononeuritis multiplex, gastrointestinal hemorrhage, purpura, polyarthralgia (polyarthritis), myalgia, and muscular weakness
2) Typical clinical course
Major clinical findings (1) and (2) develop first, followed by major clinical finding (3).
3) Major histological findings
(1) Presence of granulomatous or fibrinoid necrotizing vasculitis in microvascular associated with significant infiltration of eosinophils in the surrounding tissues
(2) Presence of extravascular granuloma
Diagnosis
1) Definite
(1) Patients with >− 1 major clinical findings of either bronchial asthma or allergic rhinitis, eosinophilia, and vasculitis and with >−1 major histological findings (allergic granulomatous angiitis)
(2) Patients with 3 major clinical findings and a typical clinical course (Churg–Strauss syndrome)
2) Probable
(1) Patient with 1 major clinical finding and 1 major histological finding (allergic granulomatous angiitis)
(2) Patients with 3 major clinical findings without typical clinical course (Churg–Strauss syndrome)
Supporting laboratory findings
(1) Leukocytosis >− 10,000 / μL)
(2) Thrombocytosis >− 400,000 / μL)
(3) Elevated serum IgE >− 600 U/mL)
(4) Positive MPO–ANCA
(5) Positive rheumatoid factor
(6) Pulmonary infiltration shadows on X–ray (these findings may not always be observed in patients)

＜ACR criteria＞
1) Asthma
History of wheezing or diffuse high–pitched rales on expiration
2) Eosinophilia
Eosinophilia＞10% on white blood cell differential count
3) Mononeuropathy or polyneuropathy
Development of mononeuropathy, multiple mononeuropathies, or polyneuropathy (i.e., glove/stoking distribution) attributable to a systemic vasculitis
4) Pulmonary infiltrates, non–fixed
Migratory or transitory pulmonary infiltrates on radiographs (not including fixed infiltrates), attributable to a systemic vasculitis
5) Paranasal sinus abnormality
History of acute or chronic paranasal sinus pain or tenderness or radiographic opacification of the paranasal sinuses
6) Extravascular eosinophils
Biopsy including artery, arteriole, or venule, showing accumulations of eosinophil in extravascular areas

If four or more of the above six items are met, the patient is considered to have Churg–Strauss syndrome (currently EGPA).

according to the Japanese criteria.

In this case, bronchoscopy showed multiple white flat lesions (white moss) in the left and right areas of the trachea and bronchi, extending to the level of the bronchi. However, Matsushima et al. reported EGPA with necrotizing airway inflammation accompanied by eosinophil infiltration and concluded that it was one of the symptoms of vasculitis observed in EGPA [8]. In this case, a biopsy of the bronchial lesion did not reveal any vasculitis or granuloma; however, it did show necrotizing airway inflammation with marked eosinophil infiltration, which resolved with treatment, suggesting that this may be one of the conditions and findings associated with EGPA.

In recent years, there have been a series of reports on the relationship between EGPA and hyper IgG4 levels and IgG4-related diseases, and EGPA is considered to be a disease similar to IgG4-related diseases [9, 10]. In this case, hyper IgG4 levels and infiltration of IgG4-positive cells were observed histologically. IgG4-RD is defined as a condition which could not be explained by other autoimmune diseases (the recent ACR/EULAR criteria [11] defines necrotizing vasculitis as an exclusion criteria) and it is reported that EGPA and IgG4-RD do not overlap [12]. On the other hand, IgG4 elevation is also present and is relevant to disease activity in MPA (microscopic polyangiitis) and GPA and the IgG4 infiltration may have indicated high disease activity because there are

evidence suggesting that IgG4 level is an indicator of disease activity in ANCA-associated vasculitis [13,14]. In addition, although cystoscopic and ureteroscopic finding were normal, kidney involvement may have been present. However, as kidney biopsy was not performed in this patient, the presence of glomerulonephritis could not be clearly demonstrated.

Systemic steroids are commonly used in the treatment of EGPA initiating with 1.0 mg/kg/day (40–60 mg/day) of PSL as an oral dose and decreasing gradually. In patients with poor prognostic factors, such as cardiac involvement, gastrointestinal involvement, alveolar hemorrhage, and central nervous system symptoms, or in those where systemic steroids alone are insufficient to improve vasculitis symptoms, combination therapy with steroids and the immunosuppressant cyclophosphamide (CY) is recommended [15]. In addition, mepolizumab (anti-IL-5) has been shown to be effective [16], and other therapies such as rituximab (anti-CD20) and omalizumab (anti-IgE) have also been reported to be effective [17]. We started remission induction therapy with steroids alone because there was no severe organ involvement, there was no FFS (Five factor score) other than age, and the patient refused to take concomitant immunosuppressive drugs due to concerns about the risk of side effects. Initially, the patient responded well to steroids and showed considerable clinical improvement, but relapsed with the reduction of steroids. At the time of relapse, the addition or combination of immunosuppressive agents was first proposed, but again, consent could not be obtained due to concerns about side effects. As the mode of relapse was mainly worsening asthma symptoms, elevated peripheral blood eosinophil count, and positive MPO-ANCA, with no worsening of vasculitis, and no appearance of severe organ involvement, mepolizumab was selected. We chose mepolizumab. In fact, mepolizumab has been shown to be effective in reducing steroid use in EGPA, and looking at the patient background of the clinical trial, a certain number of steroid-alone (immunosuppressant-naïve) patients (20–30%) were found, so the combination of mepolizumab was selected after fully explaining the risk-benefit to the patients. Following this, the condition improved again and had been stable.

In this study, we report a case of EGPA with multiple white mucosal lesions on the airway mucosa. Although mucosal lesions on the trachea and bronchi are rare in EGPA, tracheal and bronchial lesions may be one of the pathological conditions of EGPA.

Declaration of competing interest

There is no conflict of interest regarding this paper.

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