

## CASE REPORT

**Familial clustering of hypereosinophilic diseases treated with mepolizumab: a case report from Japan**

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**Running head:** Familial clustering of hypereosinophilic diseases treated with mepolizumab

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**Key words:** *anti-IL-5 antibody; eosinophilic asthma; eosinophilic granulomatosis with polyangitis; hypereosinophilic syndrome; mepolizumab*

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**Ethical disclosures:** Institutional ethics committee approved this study and written informed consent from each individual was obtained before the study.

### **Summary**

*We describe a female diagnosed with non-allergic asthma. On March 24, 2016, examination of the skin-biopsy specimen revealed dense eosinophilic infiltration, and the Fip-1-like 1-platelet-derived growth factor receptor  $\alpha$  fusion gene in peripheral blood mononuclear cells was negative. She was diagnosed with idiopathic hypereosinophilic syndrome. She was treated with intravenous methylprednisolone (MPSL), and subsequent oral MPSL. Then, she started to receive a monthly mepolizumab in June 2016, and successfully withdrew from daily use of oral MPSL. The patient has a mother diagnosed with non-allergic asthma. In February 2005, she was diagnosed with eosinophilic granulomatosis with polyangitis because of elevated antineutrophil myeloperoxidase antibodies, and the skin-biopsy specimen findings. She started to receive a monthly mepolizumab in June 2016. Corticosteroid therapy was successfully withdrawn. To our knowledge, this is the first case report suggesting mepolizumab may be a useful treatment for familial clustering of hypereosinophilic diseases.*

## Introduction

Eosinophilic granulomatosis with polyangitis (EGPA) (formerly known as Churg-Strauss syndrome) and idiopathic hypereosinophilic syndrome (HES) are rare eosinophilic disorders. Definitive diagnosis of EGPA relies on the demonstration of vasculitis in tissue-biopsy specimen (1). HES is defined by unexplained blood eosinophilia above 1500/ $\mu$ L on 2 separate occasions at least 1 month apart and evidence of end-organ involvement attributed to eosinophilia (2). Although it is quite rare that EGPA and/or HES are seen in several members of the same family, familial clustering of hypereosinophilic diseases has been reported in medical literature since the early 1900 s (3,4). In these families, the distribution of eosinophilia was suggested to involve autosomal dominant inheritance (5). On the other hand, Ota et al. (6) reported 3 siblings who suffered from marked eosinophilia, 2 of them were diagnosed with EGPA and 1 was with HES, and suggested they may be affected by another type of familial eosinophilia distinguishable from those previously described.

We describe a case of familial clustering of hypereosinophilic diseases treated with mepolizumab, a humanized IgG<sub>1</sub> monoclonal antibody that prevents human interleukin 5 (IL-5) from binding to the IL-5 receptor (7), and suggest mepolizumab may be a useful treatment for familial clustering of hypereosinophilic diseases.

## Materials and methods

Mepolizumab was administered subcutaneously every 4 week at a dose of 100 mg. Asthma Control Test (ACT) (8), peripheral blood eosinophils, forced expiratory volume in 1 second (FEV<sub>1</sub>) and drug safety were assessed at each visit; fractional exhaled nitric oxide (FeNO) was not assessed, because no significant differences were found in the DREAM trial (9). FEV<sub>1</sub> values were reported as a percentage of predicted values, using a spirometer (FUKUDA-77, Fukuda Denshi, Tokyo, Japan), and the best of 3 expiratory maneuvers was recorded. The scores in the ACT range from 5 (absence of disease control) to 25 (total disease control). The cut off value for controlled asthma (ACT  $\geq$  20) was chosen according to previous studies cut off value (10). Peripheral blood eosinophils were counted automatically by the Beckman Coulter counter (Beckman Coulter, Fullerton, CA, USA) and MAXM A/L system (Beckman Coulter). Serum levels of IgE were measured using the CAP system (Phadia, Uppsala, Sweden), and antineutrophil myeloperoxidase (MPO) antibodies were measured by an enzyme-linked immunosorbent assay (ELISA) analysis (Orgentec Diagnostika GmbH, Mainz, Germany), and the analyses and cut-off procedures were performed according to the manufacturer's instructions (reference < 3.5 U/mL). De Lavareille et al. (11) reported that serum levels of thymus and activation-regulated chemokine (TARC) may represent a precious and discriminative diagnostic tool for the patients with lymphocytic HES, and we measured TARC concentration by an ELISA kit (R&D Systems, Minneapolis, USA) as reported (12). The Fip-1-like 1-platelet-derived growth factor receptor  $\alpha$  (FIP1L1-PDGFR $\alpha$ ) fusion gene in peripheral blood mononuclear cells was analyzed by the fluorescence in situ hybridization method as reported (13).

This study was performed in accordance with the Good Clinical Practice guidelines, the ethics principles outlined in the Declaration of Helsinki 2008, in accordance with the Institutional Ethics Committee of Sutoh Hospital (IRB#20160050). Written informed consent was obtained from each individual before the study commenced.

### **Case report**

A 56-year-old female was diagnosed with bronchial asthma by the author in April 1994. She had non-allergic asthma phenotype, confirmed by low serum total IgE levels (71 IU/mL) and negative results of serum specific IgE for common inhaled allergens, including molds, and *Dermatophagoides farinae* and *petronyssinus*. The diagnosis was confirmed using the Global Initiative for Asthma (GINA) guidelines (14). Her asthma was corticosteroid-dependent and met the American Thoracic Society criteria for a diagnosis of refractory asthma (15). Her basal therapy regimen had included daily use of inhaled fluticasone 800 µg (maximum recommended dose in Japan) and inhaled salmeterol 100 µg, and near continuous ( $\geq 50$  % of year) 5 mg/day corticosteroids orally. She had experienced at least 2 or more asthma exacerbations each year that were treated with 300 mg hydrocortisone administered intravenously. Blood eosinophil count had been above 1500/ $\mu$ L from May to December 2014 with recurrent asthma exacerbations each month, which were treated with 30 mg prednisolone orally for 3 days or required a visit to the emergency department with 200 ~ 300 mg hydrocortisone intravenous administration. However, she didn't require hospitalizations. Blood eosinophil count decreased to 836/ $\mu$ L in January 2015, and asthma was well controlled with therapy

consisting of fluticasone/salmeterol 125 µg/25 µg inhaler 4 puffs/day and 5 mg prednisolone orally for a while. On September 4, 2015, she visited our clinic because of moderate asthma exacerbation. Blood eosinophil count was 1187/µL, and she was given 250 mg aminophylline and 300 mg hydrocortisone infusion. Since then, her asthma became unstable. On October 2, 2015, blood eosinophil count increased (1843/µL) with worsening of asthma requiring 300 mg hydrocortisone infusion, and since then, she was treated with fluticasone/salmeterol 250 µg/25 µg inhaler 4 puffs/day and 5 mg prednisolone orally. Eosinophil count remained above 1500/µL without clinical manifestations of end-organ involvement except asthma. On March 24, 2016, she visited the emergency department with dyspnea. She also had low-grade-fever, general fatigue, anosmia, nasal congestion, and eczematous lesions of the skin, but not peripheral limb neuropathy. Blood eosinophil count was 3416/µL. Computed tomography (CT) scan of nasal sinuses showed bilateral opacities. She was thus hospitalized for a detailed workup (**figure 1**).

Examination of the skin-biopsy specimen revealed dense eosinophilic infiltration of the dermis and subcutis. Stool microscopy did not identify any ova, cysts or parasites, and serum antibody tests for the parasites *Fasciola hepatica*, *Strongyloides* spp., *Trichinella* spp., *Taenia solium*, *Schistosoma mansoni* and *Toxocara canis* were negative. Specific IgE antibodies to *Aspergillus fumigatus* and *Candida albicans* were negative. Serum *Aspergillus* antigen was negative. Endoscopic examinations and whole body CT scan examinations were normal, and blood tests for tumor markers were negative, ruling out secondary causes of eosinophilia. Serum levels of total IgE and C-reactive protein (CRP) were 102 IU/mL and 36.6 mg/L, respectively. Antineutrophil MPO antibodies were

negative ( $< 0.5$  U/mL). Serum TARC concentration was increased to 1270 pg/mL (range in healthy controls: 7 - 470 pg/mL). The patient was negative for the FIP1L1-PDGFR fusion gene in peripheral blood mononuclear cells. However, flow cytometric analysis to look for IL-5 producing clonal lymphocyte subpopulations and bone marrow biopsy could not be performed. Given the above findings, she was diagnosed with idiopathic HES based on the criteria (2).

She was given methylprednisolone (MPSL) 500 mg/day infusion for 3 days and then oral MPSL 24 mg/day; skin lesions completely resolved, eosinophil count decreased ( $778/\mu\text{L}$ ), serum CRP levels dropped to normal levels. MPSL dose was tapered gradually to 8 mg/day. On April 15, 2016, eosinophil count was  $276/\mu\text{L}$  and she was discharged.

Her baseline medication included oral MPSL 4mg/day and fluticasone/salmeterol 125  $\mu\text{g}/25$   $\mu\text{g}$  inhaler 4 puffs/day (maximum recommended inhaled dose in Japan). She came to our clinic on June 24, 2016 as a regular visit. Blood eosinophil count, FEV<sub>1</sub> (%) value, and the ACT score were  $223/\mu\text{L}$ , 68.44 %, and 21, respectively. She started to receive a monthly mepolizumab administration. Blood eosinophil count decreased to  $44/\mu\text{L}$  on July 22, 2017. Oral MPSL was stopped, and FEV<sub>1</sub> (%) value and the ACT score gradually improved up to 76.45 % and 25 on May 10, 2019. Her asthma control has been good, and no side effects of mepolizumab have been observed until May 2019.

The patient has an 81-year-old mother, diagnosed with bronchial asthma by the author in September 1994. She had non-allergic asthma with serum total IgE level 45 IU/mL, and negative results of serum specific IgE for common inhaled allergens. The diagnosis was confirmed using the GINA guidelines (14). In February 2005, she experienced fever and weight loss with palpable purpura of the skin, arthralgia, myalgia, tenderness of four

limbs, and multiplex mononeuritis. Antineutrophil MPO antibodies were elevated (10 U/mL), and the skin-biopsy specimen revealed small-vessel vasculitis. Given these findings, she was diagnosed with EGPA based on the American College of Rheumatology criteria (1). As she had been treated for a very long time with corticosteroids, she had a very heavy burden of corticosteroids side effects, including hyperglycemia.

She visited our clinic on September 1, 2014 with recent worsening of asthma symptoms.

Blood eosinophil count was 410/ $\mu$ L, and CT scan of the sinuses confirmed chronic sinusitis. Serum total IgE level was 80 IU/mL. She was treated with fluticasone/salmeterol 125  $\mu$ g/25  $\mu$ g inhaler 4 puffs/day and 10 mg prednisolone orally.

She came to our clinic with her daughter on June 24, 2016 as a regular visit. Blood eosinophil count, glycated hemoglobin (HbA<sub>1C</sub>) level, FEV<sub>1</sub> (%) value, and the ACT score were 220/ $\mu$ L, 7.4 %, 53.96 %, and 18, respectively. She started to receive a monthly mepolizumab administration because her asthma was corticosteroid-dependent.

Then, corticosteroid therapy was successfully withdrawn in parallel with sustained reduction in blood eosinophil count and HbA<sub>1C</sub> level. FEV<sub>1</sub> (%) value and ACT score gradually improved up to 65.38 % and 25 on May 10, 2019. However, the findings of CT scan of the sinuses remained unchanged (**figure 2**). She has been stable in asthma symptoms, and no side effects of mepolizumab have been observed until May 2019.

Clinical symptoms of EGPA, such as palpable purpura of the skin, mononeuritis multiplex and chronic sinusitis did not change.

## Discussion

Eosinophilia is caused by several diseases, including allergic reaction, parasitic and viral infections, malignancies. EGPA and HES are known to be associated with peripheral blood eosinophilia. However, they are clearly distinguished from allergic reactions because they have distinctive clinical features, namely organ damage due to eosinophilia (16,17). Although EGPA and/or HES are rarely observed in the same family, familial clustering of hypereosinophilic diseases has been reported in medical literature since 1909 (3-6). In this case report, we describe a case of familial clustering of hypereosinophilic diseases, EGPA and idiopathic HES, diagnosed according to current clinical criteria (1,2), and both of them were treated with mepolizumab.

Currently available therapies for eosinophil-associated diseases including corticosteroids, and immunomodulatory and cytotoxic therapies have variable efficacy and significant toxicity, and safe and effective therapies that target eosinophils are clearly needed (18). IL-5 plays a key role on chemotaxis, differentiation, activation, and survival of eosinophils (19), and antagonism of IL-5 is considered a therapeutic target in patients with eosinophilic disorders. In November 2015, the US Food and Drug Administration (FDA) committee approved mepolizumab for use in patients older than 18 years with severe eosinophilic asthma at a dose of 100 mg administered once every 4 weeks (20), and in December 2015, the European Medicines Agency (EMA) approved a marketing authorization valid throughout the European Union as medicine under additional monitoring (21). In June 2016, mepolizumab was approved in Japan for use in patients with severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma. In December 2017, the US FDA expanded the use to

treat adult patients with EGPA, based on the results of the phase III trial report (22), with subsequent approval in May 2018 in Japan.

Advances in diagnostic approaches and therapeutic options for HES have prompted reevaluation of the definition and classification of HES. Some limitations of the diagnostic criteria established by Chusid et al. in 1975 (23) are present, and the revised-classification of HES into myeloproliferative, lymphocytic, and other forms is considered to be more useful in guiding clinical evaluation and therapeutic decisions (2). Tyrosine kinase inhibitor imatinib mesylate has been shown to be useful in myeloproliferative HES resulting from the fusion of the FIP1L1-PDGFR $\alpha$  and Fip1-like 1 genes (24,25). However, currently available therapies, including corticosteroids and imatinib, have variable efficacy and significant toxicity (26). On the other hand, mepolizumab has been suggested to be an effective and safety management of lymphocytic HES (27,28). Mepolizumab has a long-term safety for the treatment of lymphocytic HES (29,30). We describe a case of familial clustering of hypereosinophilic diseases treated with mepolizumab for 3 years in the present study. A 56-year-old female diagnosed with idiopathic HES was treated with 3 day-intravenous administrations of MPSL, and subsequent oral MPSL. After starting mepolizumab administration, she was able to stop daily therapy with oral MPSL, which was consistent with the results of a previous report (31). FEV<sub>1</sub> (%) value and the ACT score gradually improved. The limitation of this study is lack of low cytometric and bone marrow evaluations to rule out some hematological diseases in the patient, however her clinical symptoms have been stable and no side effects have been observed during the 3 years of treatment. Her clinical response points the diagnosis, and she will keep the therapy. The patient has an 81-year-old mother

diagnosed with EGPA. After beginning mepolizumab administration, she was able to stop daily therapy with oral prednisolone, which was consistent with the results of a previous report (32). In parallel with sustained reduction in blood eosinophil count, FEV<sub>1</sub> (%) value and ACT score gradually improved as reported about asthmatic findings (33,34). Her asthma symptoms have been stable and no side effects have been observed during the 3 years of the treatment. However, clinical symptoms of EGPA, with the exception of asthmatic symptoms, remained unchanged, which was consistent with previous reports (32). The lack of efficacy of mepolizumab on the non-asthmatic symptoms may be due to the dose of mepolizumab. Namely, the patient started to receive a monthly mepolizumab administration at a dose of 100 mg in June 2016, and continued it for 3 years. On the other hand, the FDA approval of mepolizumab in adult patients affected by EGPA was at a dose of 300 mg administered subcutaneously every 4 weeks, and the same dose was approved for EGPA in Japan. Further studies are needed.

Needless to say, this case report has limitations. This study is an open-label, non-controlled trial, and definite proof that mepolizumab is responsible for these improvements cannot be ensured. However, to our best knowledge, this is the first report of familial clustering of hypereosinophilic diseases, idiopathic HES and EGPA, treated with mepolizumab for 3 years, suggesting mepollizumab may be a useful treatment for familial clustering of hypereosinophilic diseases.

### **Conclusions**

This case report showed a favorable long-term safety and clinical efficacy of mepolizumab in familial clustering of hypereosinophilic diseases.

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**Declaration of interest**

The authors declare that they have no conflicts of interest, and that no funding was received for the present study.

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**Figure legends**

**Figure 1.** Clinical course of a 56-year-old female diagnosed with idiopathic hypereosinophilic syndrome. After start of monthly mepolizumab administration, she withdrew from daily use of oral methylprednisolone in parallel with stable clinical symptoms.

**Figure 2.** Clinical course of an 81-year-old female, a mother of the patient in figure 1, diagnosed with eosinophilic granulomatosis with polyangiitis. After start of monthly mepolizumab administration, she withdrew from daily use of prednisolone. In parallel with sustained reduction in blood eosinophil count and HbA<sub>1C</sub> level, FEV<sub>1</sub> (%) values and ACT scores gradually improved with mepolizumab administration.

Figure 1

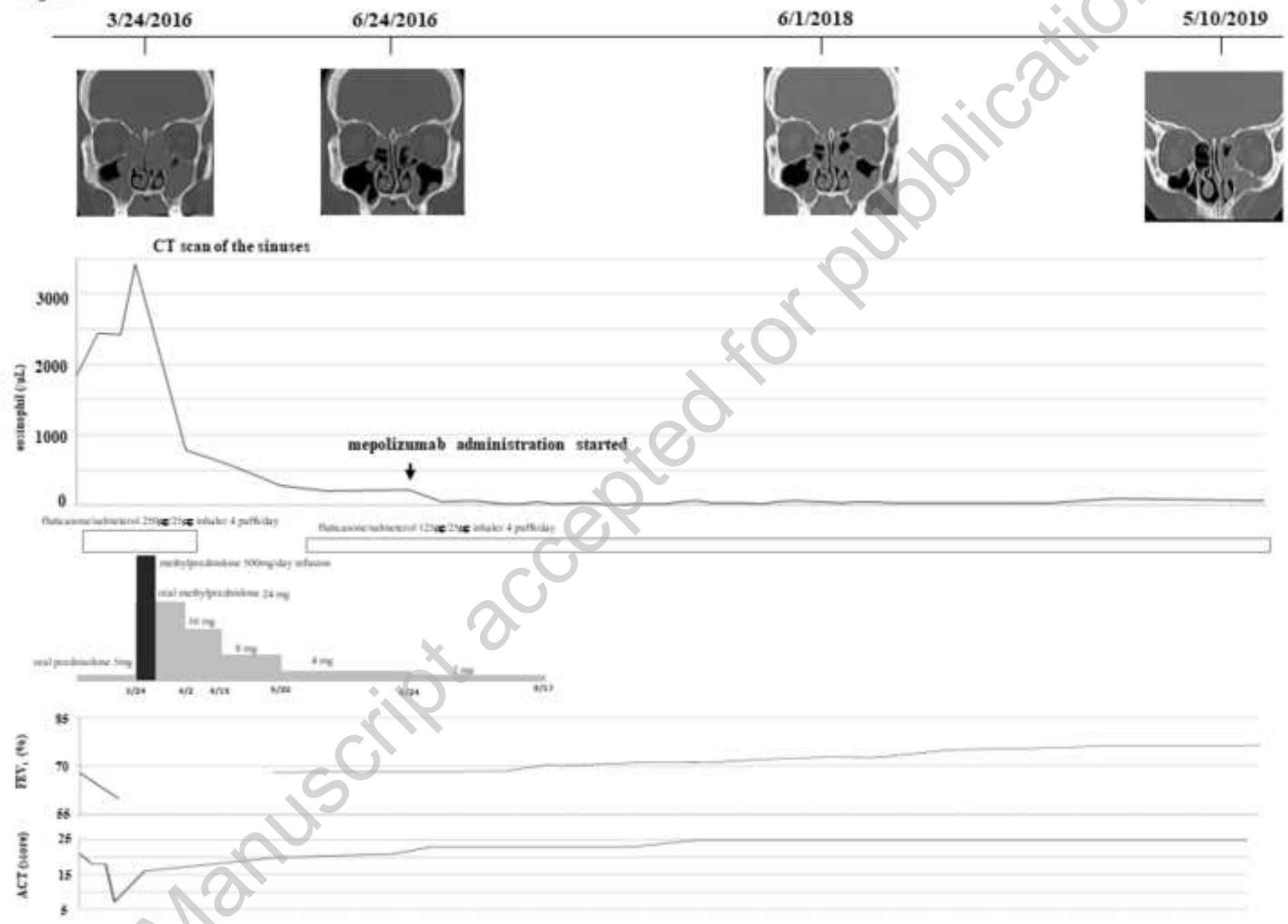
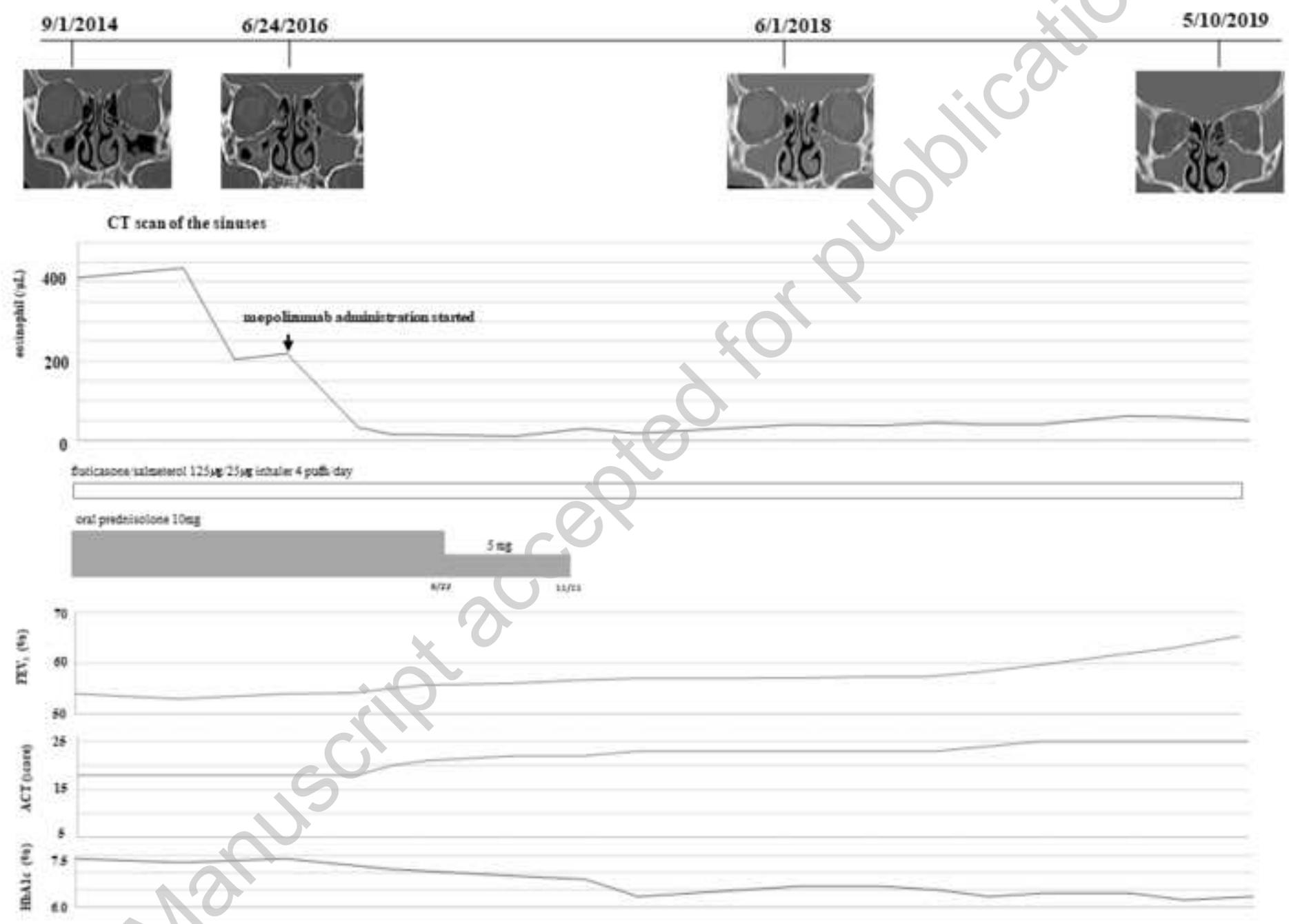


Figure 2



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