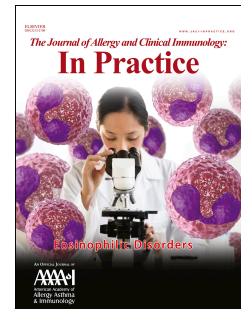


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## **Mepolizumab-responsive Kimura disease**

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Running head: Kimura disease treated with mepolizumab

## **CONFLICT OF INTEREST**

The authors have no financial conflicts of interest to disclose concerning the study.

## **KEYWORDS**

Kimura disease, IgG4-related diseases, anti-interleukin-5 antibody, mepolizumab, eosinophils, follicular helper T cells, plasma cells

## Clinical Implications

Mepolizumab, an anti-IL-5 antibody, has been determined to be effective for the treatment of a patient with Kimura disease by reducing the number of eosinophils, and IgG- and IgG4-producing plasma cells *in situ*.

Kimura disease (KD) has been identified as a rare condition in young- to middle-aged Asians, which manifests as relatively large and poorly demarcated subcutaneous nodules composed of lymphoid follicles, fibrosis, and dense eosinophil infiltration.<sup>1</sup> The presence of eosinophilia, high immunoglobulin (Ig) E levels, and fibrosis is also similarly characteristic of IgG4-related diseases (IgG4-RD).<sup>2,3</sup> Despite systemic administration and/or local injection of corticosteroids, surgical resection, or irradiation, KD is often intractable. Mepolizumab is a humanized IgG1κ monoclonal antibody (mAb) against interleukin-5 (IL-5).<sup>4</sup> In this paper, we report a case of intractable KD treated with mepolizumab and its efficacy for the reduction of IgG4-producing plasma cells (PCs).

A 42-year-old Japanese female diagnosed with KD presented to our hospital with a 2-year history of pruritic diffuse extensive indurations of both upper limbs (Figure 1A). The possibility of hypereosinophilic syndrome and hyper-IgE syndrome was excluded after a comprehensive work-up of the patient, who also had no history of susceptibility to infection and chronic eczema. She then underwent palliative surgical resection for the bilateral subcutaneous masses, but soon relapsed. Oral prednisolone administration up to 0.5 mg/kg/day over a period of 4 years was deemed ineffective. Consequently, we decided to administer mepolizumab after a washing-out period of prednisolone. Pre-treatment skin biopsy revealed prominent lymphoid aggregates with reactive germinal follicles, fibrosis, and dense eosinophil infiltration (Figure 1B). Interestingly, an infiltration of IgG- and IgG4-positive PCs was observed (Figure 1C). The ratio of IgG4-positive PCs to IgG-positive PCs was 42.8%. Laboratory tests were as follows: a total white blood cell count of 6,300/μl with eosinophilia (32%), serum IgE of 24,145.3

IU/ml (normal < 311.6 IU/ml), serum thymus and activation-regulated chemokine (TARC) of 7,030 pg/ml (normal < 450 pg/mL), serum IgG4 of 31 mg/dL (normal < 117 mg/dL), and undetectable serum IL-4. All other serum parameters were within normal limits. Fat-suppressed coronal T2-weighted magnetic resonance imaging (MRI) of the upper limb revealed diffuse subcutaneous masses (Figure 2A). Collectively, our case was consistent with KD. Moreover, when the diagnostic criteria of IgG4-RD were applied to our case, the diagnosis was found to be “probable” IgG4-RD.

After providing written informed consent, the patient was given 300 mg of anti-IL-5 humanized mAb (mepolizumab; GlaxoSmithKline, Harlow, UK) subcutaneously once a month for 8 months. After the treatment, a dramatic regression of the clinically indurated masses was observed, accompanied by a reduction in MRI intensity, but there was no improvement in the swelling and maximum circumference of both limbs (Figures 1A and 2A). The eosinophilia and high serum IL-5 levels improved over time, but the high serum IgE levels did not (Figures 2B–D). The remaining subcutaneous masses were totally excised. Eosinophils were almost absent in the resected mass, while the mass was replaced with fibrosis (Figures 1B and 1D), suggesting that this fibrosis caused unaltered swelling and maximum circumference of both limbs. Interestingly, mepolizumab administration significantly reduced the number of IgG- and IgG4-positive PCs *in situ* (Figures 1C and 1E). Follicular helper T cells ( $T_{FH}$ ) have been known to promote eosinophil recruitment<sup>5</sup> and fibrosis.<sup>6</sup> Prior to treatment, approximately half of the  $CD4^+$  T cells in lymphoid follicles expressed CXCR5 or PD-1, suggesting a possibility that some of these  $CD4^+$  T cells were  $T_{FH}$ . It is worth noting that there was no reduction of these putative  $T_{FH}$  after treatment (data not shown). After total excision, mepolizumab administration was continued without relapse 6 months after.

Given the preferential development of KD in the head and neck, bilateral upper limb involvement is quite rare.<sup>1</sup> We reported mepolizumab-mediated drastic eosinophil reduction in the circulation and subcutaneous mass of a patient with KD. Despite

eosinophil disappearance in the mass, fibrosis was persistent. This may be because our patient had chronic KD for 6 years before mepolizumab administration. Long-lasting local inflammation may result in persistent fibrosis. Conversely, early intervention with mepolizumab might have changed the result.  $T_{FH}$  facilitate fibrosis and B cell differentiation, leading to an increase of IgG1- and IgE-producing memory B cells and PCs.<sup>7</sup> We implied the presence of  $T_{FH}$  in KD and their unresponsiveness to mepolizumab. The persistent fibrosis and the stable serum IgE levels during treatment must be primarily mediated by long-lasting local inflammation and long-lived PCs, respectively. Besides, the persistent  $T_{FH}$  may facilitate these responses. Moreover, because  $T_{FH}$  promote eosinophil recruitment, persistent of this may cause KD relapse after the discontinuation of mepolizumab.

In murine skin transplantation models, intraperitoneal injection of anti-IL-5 mAb has reportedly reduced the number of alloreactive PCs in the bone marrow by suppressing the production of an eosinophil-derived a proliferation-inducing ligand (APRIL) and IL-6,<sup>8</sup> both of which are crucial for long-term maintenance of PCs. However, serum APRIL and IL-6 levels of the patient were not altered during the course (data not shown). Therefore, the underlying mechanism by which mepolizumab reduced the number of IgG- and IgG4-producing PCs remains to be unclear.

A case report demonstrated the efficacy of subcutaneous administration of 100 mg of mepolizumab once a month together with continuous oral administration of azathioprine, mesalamine, and anti-IgE medications for the treatment of KD.<sup>9</sup> In this present study, we report the efficacy of monotherapy of 300 mg of mepolizumab in a patient with KD. Besides eosinophils, IgG4-positive PCs, but not  $T_{FH}$ , were also determined to be reduced *in situ*. In this context, mepolizumab might be a promising option for the treatment of patients with KD and IgG4-RD. Lastly, early intervention with mepolizumab might prevent secondary fibrosis caused by KD.

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**ETHICAL APPROVAL**

This study was approved by the Institutional Review Board of Yamanashi University Hospital.

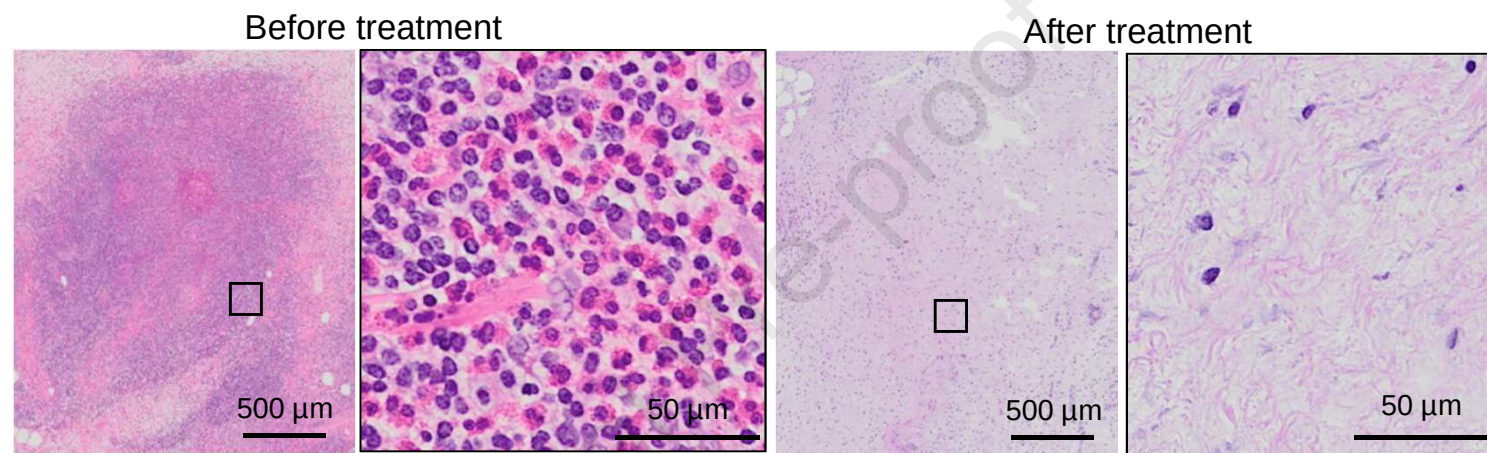
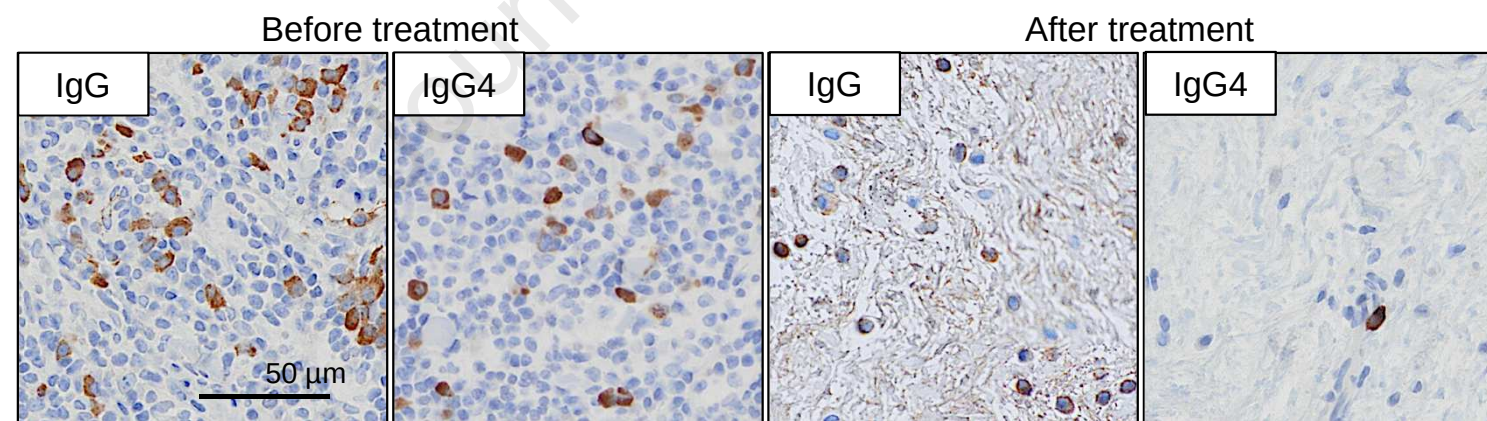
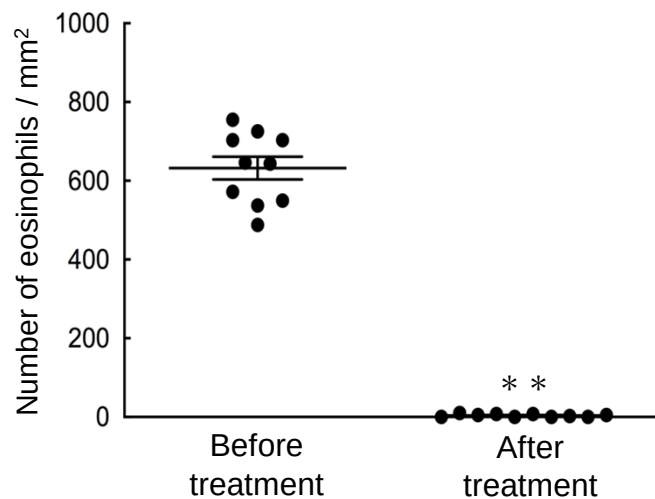
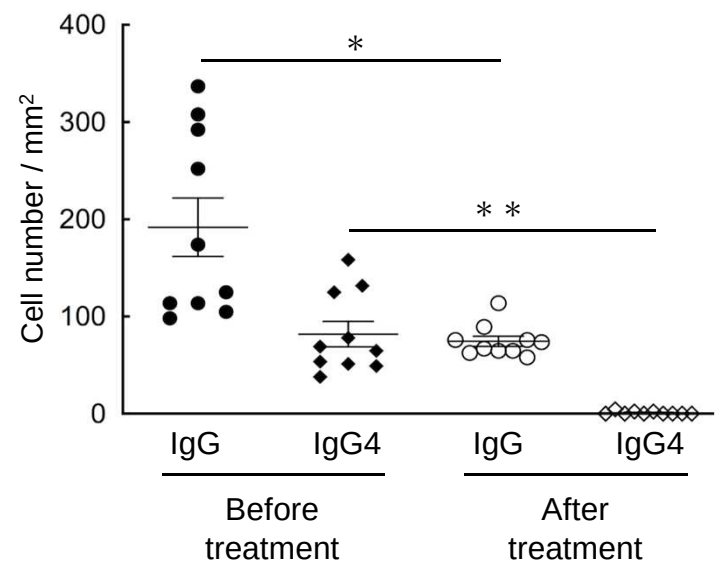
**REFERENCES**

1. Marka A, Cowdrey MCE, Carter JB, Lansigan F, Yan S, LeBlanc RE. Angiolymphoid hyperplasia with eosinophilia and Kimura disease overlap, with evidence of diffuse visceral involvement. *J Cutan Pathol* 2019; 46:138-42.
2. Tokura Y, Yagi H, Yanaguchi H, Majima Y, Kasuya A, Ito T, et al. IgG4-related skin disease. *Br J Dermatol* 2014; 171:959-67.
3. Liu L, Chen Y, Fang Z, Kong J, Wu X, Zhang Z. Kimura's disease or IgG4-related disease? A case-based review. *Clin Rheumatol* 2015; 34:385-9.
4. Gnanakumaran G, Babu KS. Technology evaluation: mepolizumab, GlaxoSmithKline. *Curr Opin Mol Ther* 2003; 5:321-5.
5. Chen X, Xu Z, Wei C, Yang X, Xu L, Zhou S, et al. Follicular helper T cells recruit eosinophils into host liver by producing CXCL12 during *Schistosoma japonicum* infection. *J Cell Mol Med* 2020; 24:2566-72.
6. Taylor DK, Mittereder N, Kuta E, Delaney T, Burwell T, Dacosta K, et al. T follicular helper-like cells contribute to skin fibrosis. *Sci Transl Med* 2018; 10.
7. Qi H. T follicular helper cells in space-time. *Nat Rev Immunol* 2016; 16:612-25.
8. Redfield RR, Rodriguez E, Luo Y, Rostami S, Parsons RF, Noorchashm H, et al. Interleukin 5 immunotherapy depletes alloreactive plasma cells. *J Surg Res* 2014; 187:310-5.
9. Al Shammari F, Nasiri A, Alkhathami M, Alawfi F, Alfifi M, Al Otaibi E. Mepolizumab as an effective treatment for Kimura's disease associated with ulcerative colitis: A case report. *J Family Med Prim Care*. 2019;8(9):3028-3031.

**FIGURE LEGENDS**

**FIGURE 1.** (A) Clinical images of the upper limbs before (left panels) and after (right panels) mepolizumab administration. The upper and lower panels are the right and left upper limbs, respectively. The scars on bilateral upper limbs were made by palliative surgical resection. (B) H&E staining (low and high magnification) of the mass taken before and after mepolizumab administration. (C) Immunohistochemistry for IgG and IgG4 in the mass taken before and after mepolizumab administration. (D) Eosinophil number in 10 randomized areas (counted in magnification 100×) of the mass before and after mepolizumab administration. (E) Number of IgG- or IgG4-positive cells in 10 randomized areas (counted in magnification 100×) of the mass before and after mepolizumab administration. \* $p < 0.05$ , \*\* $p < 0.01$ .

**FIGURE 2.** (A) The left panels are fat-suppressed coronal T2-weighted MRIs of the upper limb before and after mepolizumab administration. The right graph represents the maximum circumference of both upper limbs during the course of treatment. (B) Number and percentage of eosinophils, (C) serum IL-5 levels, and (D) serum IgE levels in the peripheral blood during the course.

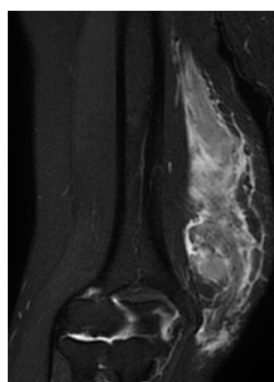
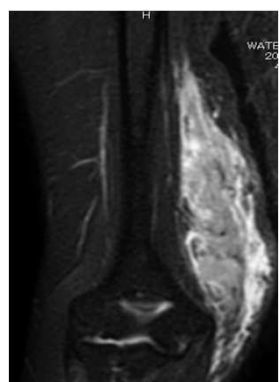
**FIGURE 1****A****B****C****D****E**

# FIGURE 2

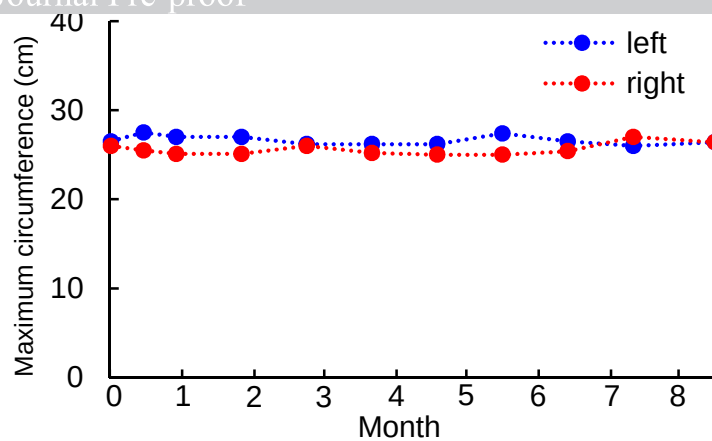
A

Before treatment

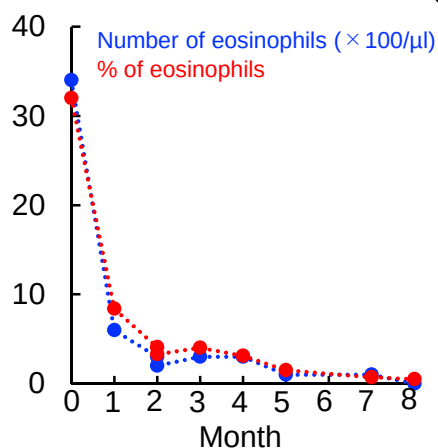
After treatment



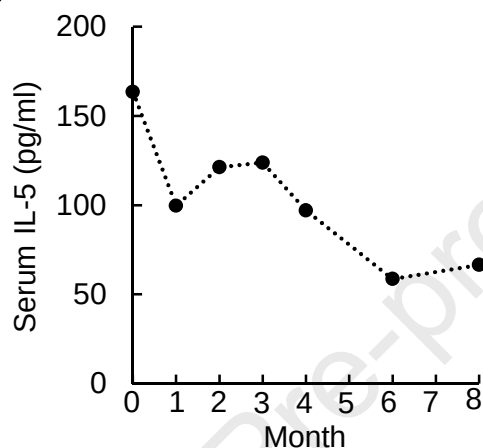
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B



C



D

