Increased blood group 2 innate lymphoid cells contribute to blood eosinophilia, elevated IgE, and itching in Kimura disease

Ichiro Tojima[1], Shiori Hara[1], Takuya Murao[1], Keigo Nakamura[1], Sayuri Yamamoto[1], Hiroyuki Arai[1], Hideaki Kouzaki[1], Shino Shimizu[1], and Takeshi Shimizu[1]

[1]Shiga University of Medical Science

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Title:

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Ichiro Tojima, MD, PhD, Shiori Hara, MD, Takuya Murao, MD, Keigo Nakamura, MD, Sayuri Yamamoto, MD, Hiroyuki Arai, MD, Hideaki Kouzaki, MD, PhD, Shino Shimizu, MD, PhD, Takeshi Shimizu, MD, PhD

Department of Otorhinolaryngology, Shiga University of Medical Science, Otsu, Japan

Correspondence

Ichiro Tojima, MD, PhD

Department of Otorhinolaryngology, Shiga University of Medical Science

Seta-Tsukinowa, Otsu, Shiga 520-2192, Japan

Tel: +81-77-548-2261

Fax: +81-77-548-2783

E-mail: itirotz@belle.shiga-med.ac.jp

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Text

To the editor:

Kimura disease (KD) is a rare, chronic inflammatory disorder characterized by subcutaneous mass lesions with itching and tissue eosinophilia in the head and neck region.[1] The disease is observed predominantly in young men of Asian countries, and although the mass lesions may be eradicated by surgery and steroid therapy, the disease frequently recurs. Laboratory tests show marked blood eosinophilia and elevated serum IgE; however, the precise etiology of this disease is unknown. Several researchers have reported the role of type 2 cytokines in the pathogenesis of KD. IL-4 and IL-5 expressing mast cells and T cells are increased in local lesions[2], and the mRNA expression of IL-4, IL-5, and IL-13 in peripheral blood mononuclear cells (PBMCs) is correlated with the number of peripheral eosinophils in KD.[3] IL-4 and IL-13 directly stimulate sensory neurons via IL-4 receptor subunit-α (IL-4Rα),[4] and consequently these cytokines may be more important than histamine for the chronic itching.[5]

Group 2 innate lymphoid cells (ILC2s) have been recently identified as important effector cells for eosinophilic inflammation such as allergic rhinitis (AR), chronic rhinosinusitis, asthma, atopic dermatitis, and eosinophilic esophagitis.[6] ILC2s play critical roles in the induction of type 2 inflammation through the production of IL-4, IL-5, and IL-13, in response to epithelium-derived cytokines, IL-33 and IL-25, and other mediators such as prostaglandin D_2(PGD_2) and cysteinyl leukotrienes (cysLTs; LTC_4, LTD_4, and LTE_4).[7, 8] We hypothesized that ILC2s may play a role in the pathogenesis of KD by regulating eosinophil infiltration, IgE synthesis, and chronic itching. In the present study, the prevalence of blood ILC2s was analyzed in a KD patient, and the effects of clinical interventions, specifically surgery and steroid therapy, were examined.

A 41-year-old man was referred to our university hospital complaining of a 7-year history of swelling and itching on his right upper neck. On examination, a 7.0 X 5.8 cm hard mass was found in his right parotid area. Magnetic resonance imaging (MRI) and computed tomography showed a 6.0 X 5.5 cm mass in his right parotid gland. Laboratory data revealed increased blood eosinophilia (15.9% of total leukocytes) and high serum IgE levels (1434 IU/mL) (Table S1). Serum salivary amylase (79 U/L) was normal, and autoantibodies such as PR3-ANCA, MPO-ANCA, anti-SS-A/Ro, and anti-SS-B/La were negative.

ILC2s were identified as Lineage$^-$CD45$^+$ CD127$^+$CRTH2$^+$ cells in PBMCs (Figure S1). The prevalence of blood ILC2s in this patient (4.9% of CD45$^+$ cells) was about 10 times higher than those in control subjects and patients with house dust mite (HDM)-induced AR (0.45 $\pm$ 0.1% and 0.6 $\pm$ 0.1%, respectively, Figure 1A, B). A significant positive correlation between blood ILC2s and blood eosinophils (R = 0.91, $P = 0.045$, Figure 1C), and a positive correlation between blood ILC2s and serum IgE levels (R = 0.95, $P = 0.053$, Figure 1D) were found in all study subjects. To examine the ability to produce IL-5, IL-13, and IL-4 from ILC2s, sorted PBMC-derived ILC2s from this patient were stimulated with or without IL-33, PGD_2, LTC_4, LTD_4, and LTE_4. PBMC-derived ILC2s constitutively produced certain amounts of IL-5 and IL-13, which were increased in response to IL-33, PGD_2, LTC_4, LTD_4, or LTE_4(Figure 1E, F). Although the amount was low, ILC2s also produced IL-4 in response to LTC_4, LTD_4, or LTE_4 (Figure 1G). These cysLTs are synthesized by eosinophils in response to IL-5 and IL-13.[9] These results indicate that increased blood ILC2s exacerbate eosinophilic inflammation through the production of IL-5, IL-13, and IL-4 in KD.

The visual analog scale (VAS) scores of itching (10/10) and general distress (10/10) were very severe, and a right superficial parotidectomy was performed. Histological examination revealed the characteristic features of KD: lymphoid hyperplasia with reactive germinal centers and massive eosinophil infiltrations (380 cells/HPF) with microabscess formation (Figure 1H). A normal parotid gland lacks a germinal center and contains few eosinophils (Figure S2). After surgery, we started the patient on 125 mg/day (2 mg/kg) prednisolone (PSL) with tapering for one month, and noted that the postoperative course was uneventful. The prevalence of blood ILC2s (1.1%) and blood eosinophils (0.1%) were decreased one day after surgery (Fiureg 2A). These parameters remained low for one month during the steroid therapy, and the VAS scores of itching and general distress completely dissipated (0/10, Figure 2A, B).

Three years after surgery, the patient complained about swelling with itching on his right parotid area again (Figure 2B, C). Five years after surgery, the VAS scores worsened (itching 9/10 and general distress 8/10), and the prevalence of blood ILC2s (5.4%), blood eosinophilia (17%), and the parotid gland size were increased (Figure 2A-D). Oral PSL therapy (30 mg/day, 0.5 mg/kg) with tapering for one month ameliorated the parotid gland swelling and the VAS scores (itching 1.5/10 and general distress 3/10). The prevalence of blood ILC2s (1.6%), blood eosinophilia (11.7%), and serum IgE levels (509.5 IU/mL) were also decreased (Figure 2A, B, and D). After stopping the PSL therapy, the prevalence of blood ILC2s, blood eosinophilia, and the VAS scores gradually increased (Figure 2A, B). These findings suggest that effective clinical interventions such as surgery and systemic steroid therapy ameliorate the prevalence of blood ILC2s, blood eosinophilia, and clinical symptoms in KD.

This is the first report showing the prevalence of blood ILC2s in a KD patient, which was increased compared to control subjects and patients with HDM-induced AR. KD-derived blood ILC2s produced IL-5, IL-13, and IL-4 in response to IL-33, PGD_2, LTC_4, LTD_4, or LTE_4. These type 2 cytokines may play an important role in the pathogenesis of KD by regulating eosinophil infiltration, IgE production, and chronic itching. Surgical

removal of mass lesions and systemic steroid therapy ameliorated clinical symptoms along with decreases in blood ILC2s, blood eosinophilia, and serum IgE levels. Upon recurrence of the disease, blood ILC2s and blood eosinophilia were observed to be increased. These results indicate that increased ILC2s contribute to blood eosinophilia, elevated serum IgE levels, and chronic itching through the production of type 2 cytokines.

KD is a rare disease and we have encountered only one case during the last 15 years. Blood eosinophilia, elevated serum IgE levels, and chronic itching are commonly observed in KD patients, and we revealed that increased blood ILC2s might contribute to these characteristic features of KD. Although the etiology of KD remains unclear, regulation of ILC2s may have a novel therapeutic potential for intractable KD. We hope that these findings will be confirmed and developed in subsequent investigations.

CONFLICTS OF INTEREST

The authors declare that they have no relevant conflicts of interest.

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Ichiro Tojima

Shiori Hara

Takuya Murao

Keigo Nakamura

Sayuri Yamamoto

Hiroyuki Arai

Hideaki Kouzaki

Shino Shimizu

Takeshi Shimizu

Department of Otorhinolaryngology, Shiga University of Medical Science, Otsu, Shiga, Japan. E-mail: itirotz@belle.shiga-med.ac.jp.

Correspondence

Ichiro Tojima, Department of Otorhinolaryngology, Shiga University of Medical Science, Otsu, Shiga, Japan, 5202192.

E-mail: itirotz@belle.shiga-med.ac.jp

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Figure legends

Figure 1

Prevalence, correlation, and cytokine production of blood ILC2s in the KD patient. (A) Representative FACS scattergrams for blood ILC2s (Lineage$^-$ CD45$^+$CD127$^+$ CRTH2$^+$ cells, red box) in PBMCs from a control subject, a patient with HDM-induced AR, and a KD patient. (B) Prevalence of blood ILC2s in total CD45$^+$cells. (C-D) Correlation between the prevalence of blood ILC2s and the percentage of blood eosinophils in total leukocytes (C), and serum IgE levels (D) in all study subjects. (E–G) Effects of IL-33 (30 ng/mL), PGD_2 (1 μM), LTC_4 (50 nM), LTD_4 (50 nM), or LTE_4 (50 nM) on the production of IL-5 (E), IL-13 (F), and IL-4 (G) from cultured KD-derived blood ILC2s. Sorted ILC2s were cultured with IL-2 (50 ng/mL).$^*P < 0.05$;$^{**}P < 0.01$ compared with the control medium (IL-2 only). (H) Histological examination of the right superficial parotid gland from a KD patient shows lymphoid hyperplasia with reactive germinal centers (arrows) and massive eosinophil infiltrations with microabscess formation. Hematoxylin and eosin stain, Bar = 100 μm.

Figure 2

Changes in the prevalence of blood ILC2s, blood eosinophilia, clinical symptoms, MRI findings, and photographs before and after surgery and steroid therapy. (A) Changes in the prevalence of blood ILC2s and the percentage of blood eosinophils. PSL, prednisolone; d, day; w, week; m, month; y, year. (B) Changes in the prevalence of ILC2s and the VAS scores of itching and general distress. (C) Axial and coronal MRI (T2 weighted images) show a mass lesion in the right parotid gland (arrows). (D) Swelling of right parotid area (arrows).

Figure S1

Isolation of PBMC-derived ILC2s from the patient with KD. Lineage$^-$ CD45$^+$CD127$^+$ CRTH2$^+$ cells were sorted using FACSAria.

Figure S2

Histological examination of a normal parotid gland from a patient with pleomorphic adenoma shows no germinal centers and few eosinophils. Hematoxylin and eosin stain, Bar = 100 μm.

Figure 1

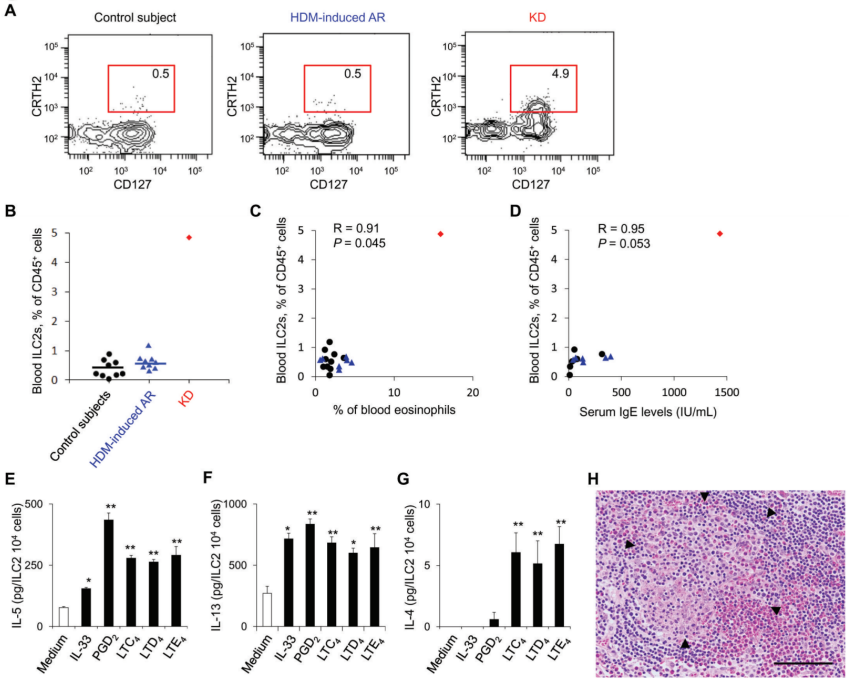

Figure 2