Increased blood group 2 innate lymphoid cells are associated with the clinical severity of Kimura disease.

Allergology International xxx (xxxx) xxx

Contents lists available at ScienceDirect

Allergology International

journal homepage: http://www.elsevier.com/locate/alit

Letter to the Editor

Increased blood group 2 innate lymphoid cells are associated with the clinical severity of Kimura disease

Dear Editor,

Kimura disease (KD) is a chronic inflammatory disorder characterized by general itching, subcutaneous head and neck mass lesions with tissue eosinophilia, blood eosinophilia, and elevated serum IgE levels.[1] KD is a rare disorder, and only 238 cases have been reported worldwide in the last 30 years.[2] Although the mass lesions are eradicated by surgery and steroid therapy, the disease frequently recurs. The precise etiology of this disease is unknown. Several researchers have reported the role of type 2 cytokines in the pathogenesis of KD; interleukin (IL) -4- and IL-5-expressing mast cells and T cells accumulate in local lesions,[3] and the mRNA expressions encoding IL-4, IL-5, and IL-13 in peripheral blood mononuclear cells (PBMCs) were positively correlated with the number of blood eosinophils.[4]

Group 2 innate lymphoid cells (ILC2s) have been identified as important effector cells for eosinophilic airway inflammation such as allergic rhinitis (AR), chronic rhinosinusitis, and asthma.[5] ILC2s in mucosal tissues play critical roles in the induction of type 2 inflammation through the production of IL-4, IL-5, and IL-13 in response to various mediators such as prostaglandin (PG) D_2 and leukotriene (LT) C_4, D_4, and E_4[5] released by eosinophils and mast cells.[6,7] However, the role of blood ILC2s in eosinophilic inflammation, such as KD, has not been well understood. We examined the prevalence of blood ILC2s; their ability to produce IL-4, IL-5, IL-13, and IL-31; and serum concentrations of these type 2 cytokines in patients with KD compared with those in patients with HDM-induced AR and control subjects (Supplementary Methods).

Clinical data for the study subjects are listed in Supplementary Table 1. The prevalence of blood ILC2s in patients with KD ($2.35 \pm 0.90\%$ of $CD45^+$ cells) was eight times and six times higher than those in control subjects ($0.29 \pm 0.03\%$) and in patients with AR ($0.37 \pm 0.04\%$, Fig. 1A, Supplementary Fig. 1), respectively. Correlation analysis in all study subjects revealed a strong positive correlation between the prevalence of ILC2s and percentage of eosinophils in blood (Fig. 1B), and a weak positive correlation between blood ILC2 prevalence and serum IgE levels (Fig. 1C).

Serum IL-13 levels were elevated in patients with KD compared with those in patients with AR and control subjects (Fig. 1D). Most of the serum IL-5 levels were below the detection limit, and serum IL-4 and TSLP levels were not changed (Supplementary Fig. 2). Serum IL-31 levels were significantly decreased in patients with KD compared with those in patients with AR (Fig. 1E). There was a weak positive correlation between blood ILC2 prevalence and serum IL-13 levels (Fig. 1F), however, there was no correlation between blood ILC2 prevalence and serum levels of IL-4 or IL-31 (Supplementary Fig. 3A, B).

ILC2s were incubated (starting immediately after sorting) with PGD_2 or LTD_4 for 7 days, and PGD_2 or LTD_4 stimulated the productions of IL-5, IL-13, and IL-4 by ILC2s derived from patients with KD; the productions of IL-5, IL-13 and IL-4 were significantly increased when compared with those by ILC2s derived from patients with AR and control subjects (Fig. 1G, Supplementary Fig. 4). ILC2s did not produce detectable levels of IL-31.

The most widely used treatments for KD are surgical resection of the mass lesions and systemic steroid therapy.[2] Systemic steroid therapy has a transient effect caused by its anti-inflammatory actions. PGD_2-and LTD_4-induced productions of IL-5 and IL-13 were significantly inhibited by dexamethasone dose-dependently (Supplementary Fig. 5).

We presented a severe case of 41-year-old man with KD, complaining of a 7-year history of general itching and swelling on his right upper neck. A 7.0 cm $\times$ 5.8 cm hard mass was found in his right parotid area. Laboratory data revealed blood eosinophilia (15.9% of total leukocytes) and high serum IgE level (1434 IU/mL). His blood ILC2 prevalence was elevated (4.9% of $CD45^+$ cells). The VAS scores of general itching (10/10) and distress (10/10) were very severe, and a right superficial parotidectomy was performed. Histological examination revealed the characteristic features of KD. After surgery, we started the patient on 125 mg/day (2 mg/kg) prednisolone (PSL) with subsequent tapering for one month, and the postoperative course was uneventful. The prevalence of blood ILC2s and blood eosinophils were decreased one day after surgery. These parameters remained low for one month during steroid therapy, and clinical symptoms were eliminated completely (Fig. 2A, B).

Three to five years after surgery, the VAS scores were getting worsened, and the patient again exhibited high blood ILC2 prevalence, blood eosinophilia, high serum IgE level (1009 IU/mL), and parotid swelling (Fig. 2A–D). Oral PSL treatment (30 mg/day, 0.5 mg/kg) with tapering ameliorated the parotid swelling and the VAS scores. Blood ILC2 prevalence, blood eosinophilia, and serum IgE level (509.5 IU/mL) were also decreased. After stopping the PSL treatment, these parameters gradually increased again.

This is the first report showing the increased prevalence of blood ILC2s and their increased ability to produce IL-5, IL-13, and IL-4 in patients with KD. Serum concentrations of IL-13 were elevated in patients with KD, and blood ILC2 prevalence was positively correlated with serum concentrations of IL-13,

Peer review under responsibility of Japanese Society of Allergology.

https://doi.org/10.1016/j.alit.2022.10.002

Please cite this article as: Tojima I et al., Increased blood group 2 innate lymphoid cells are associated with the clinical severity of Kimura disease, Allergology International, https://doi.org/10.1016/j.alit.2022.10.002

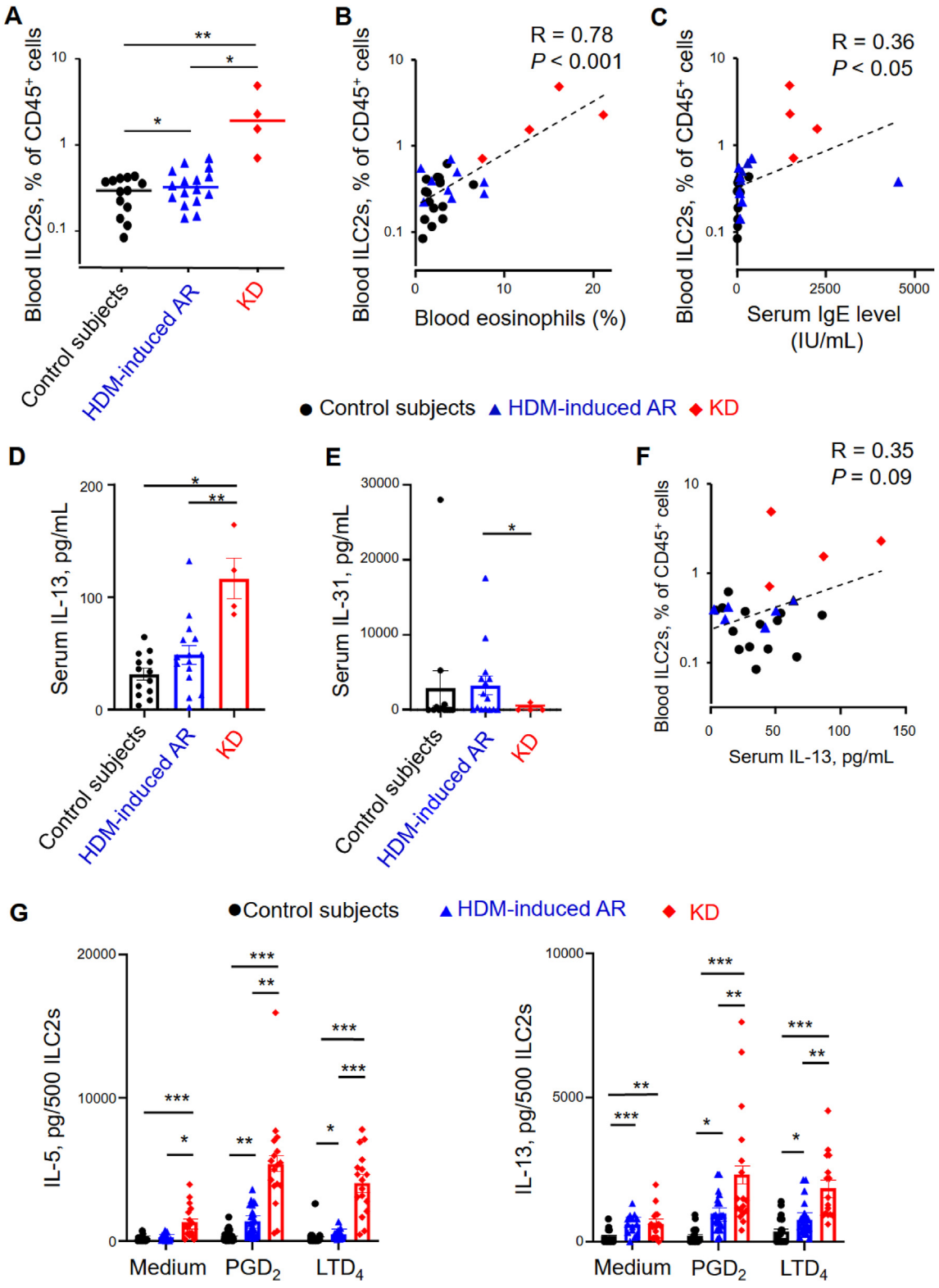

Fig. 1. The prevalence of blood ILC2s, serum concentrations of IL-13 and IL-31, and ILC2-induced IL-5 and IL-13 productions in control subjects, patients with house dust mite (HDM) -induced allergic rhinitis (AR), and patients with Kimura disease (KD). **A**, The prevalence of blood ILC2s in control subjects, patients with HDM-induced AR, and patients with KD. **B** and **C**, Correlation between blood ILC2 prevalence and the percentage of blood eosinophils (**B**) and serum IgE levels (**C**) in all study subjects. **D** and **E**, Serum concentrations of IL-13 (**D**) and IL-31 (**E**) in control subjects, patients with HDM-induced AR, and patients with KD. **F**, Correlation between blood ILC2 prevalence and serum concentrations of IL-13. **G**, The production of IL-5 and IL-13 from blood ILC2s derived from control subjects, patients with HDM-induced AR, and patients with KD. Data are shown as the mean ± SEM. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$.

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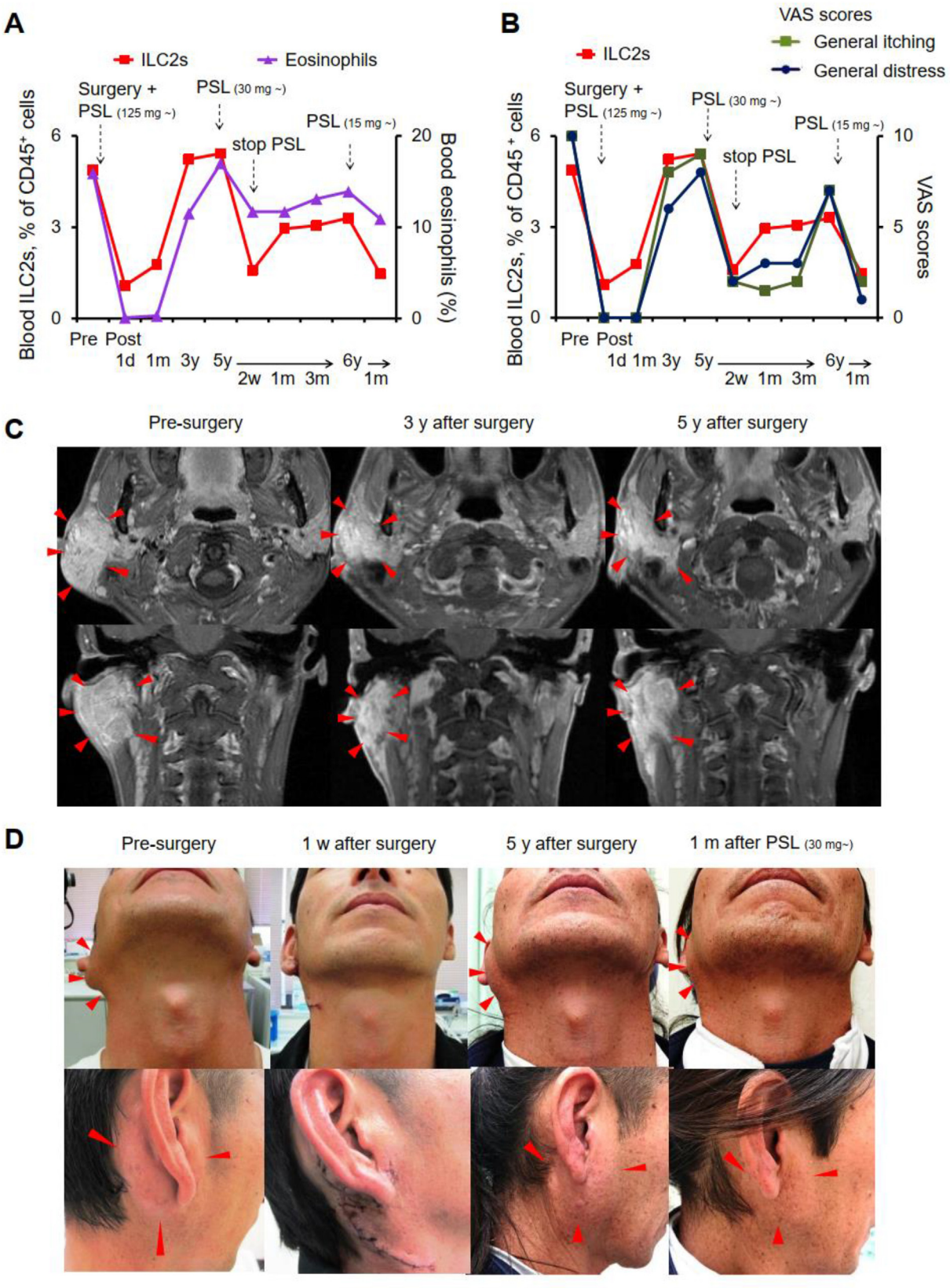

Fig. 2. Changes in the prevalence of blood ILC2s, blood eosinophilia, clinical symptoms, MRI findings, and photographs in a representative severe case of KD before and after surgery and steroid therapy. **A**, Changes in blood ILC2 prevalence and the percentage of blood eosinophils. PSL, prednisolone; d, day; w, week; m, month; y, year. **B**, Changes in blood ILC2 prevalence and the visual analog scale (VAS) scores of general itching and distress. **C**, Changes in axial and coronal MRI (T2-weighted images) showing a mass lesion in the right parotid area (red arrows). **D**, Changes in swelling of right parotid area (red arrows).

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blood eosinophilia, and serum IgE levels. In our severe case, resection of mass lesion and systemic steroid treatment ameliorated clinical symptoms, with concomitant decreases of blood ILC2s, blood eosinophilia, and serum IgE levels. These results suggest that the increased blood ILC2s and their ability to produce type 2 cytokines may be involved in blood eosinophilia, elevated serum IgE levels, and clinical symptoms such as general itching, in KD patients. The role of tissue ILC2s in the mass lesion of KD is also an important research subject for further studies.

Itching is the most frequent symptom in KD.[2] IL-4, IL-13, and IL-31 stimulate sensory neurons,[8] and consequently, these cytokines are more critical than histamine for itching. Elevated serum IL-31 levels were positively correlated with the severity of atopic dermatitis[9] and bronchial asthma.[10] In the present study, serum IL-13 levels were elevated, and blood ILC2 produced a large amount of IL-13. However, serum IL-31 levels were decreased, and blood ILC2s did not produce IL-31. These results indicate that ILC2-derived IL-13 may be responsible for itching in KD. IL-31 is produced primarily by Th2 cells, and the function of Th2 cells in KD will be the subject of further studies.

Acknowledgements

This research was supported, in part, by the Japan Society for the Promotion of Science (JSPS; Grant Numbers 17K16908 and 20K09754). We thank the staff of the central research laboratory of Shiga University of Medical Science for their important contributions to the completion of this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.alit.2022.10.002.

Conflict of interest

The authors have no conflict of interest to declare.

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Received 8 June 2022
Received in revised form 14 September 2022
Accepted 22 September 2022
Available online xxx