



Letter

Eosinophilic esophagitis associated with *Cynanchum wilfordii*

Eosinophilic esophagitis (EoE) is a chronic esophageal inflammatory disease characterized by eosinophilic infiltration into the esophageal epithelium.¹ The cause of EoE is not well understood, but a likely cause involves antigenic exposure to food allergens and/or aeroallergens that induces a response in genetically predisposed individuals.² *Cynanchum wilfordii* belongs to the family Asclepiadaceae and is distributed in eastern Asia. Its tuberous root has been used as traditional herbal medicine. It recently received attention as a health supplement food, and EstroG-100 (herbal extract containing *C wilfordii*) was approved by the US Food and Drug Administration as a new dietary supplement. *Cynanchum wilfordii* significantly alleviated menopausal symptoms of perimenopausal women without any reported serious side effects, including allergic reactions.³ We describe 1 case of EoE after repeated use of *C wilfordii* for health promotion purposes.

A 52-year-old woman was referred to our allergy clinic to evaluate the cause of her EoE. She had epigastric pain and heartburn for 2 months. She had started taking health supplement capsules containing *C wilfordii* 3 months previously. At first, after 2 to 3 weeks of intake, she developed epigastric pain and then stopped taking the capsules. During the 1 to 2 weeks of discontinuation, her symptoms were relieved. However, the epigastric discomfort worsened a few days after she started taking the capsules again. Therefore, she visited a local clinic and underwent esophagogastroscope, during which diffuse whitish mucosal plaques were seen. Pathologic findings showed diffuse eosinophilic infiltrations in the midesophageal mucosa (>100 /high-power field).

She had no history of allergic disease or other medical conditions. Her epigastric clamping pain and chest discomfort disappeared after she stopped taking *C wilfordii*. Skin prick testing for common inhalant allergens and food allergens showed negative results except for *Dermatophagoides farinae*. Her peripheral blood eosinophil count was increased slightly ($594/\mu\text{L}$). The total IgE level, measured by ImmunoCAP (Phadia AB, Uppsala, Sweden), was 99.7 IU/mL . To evaluate the causative allergen, skin prick testing and intradermal testing were performed using aspirated contents from the soft capsules that she took. An additional basophil activation test (BAT) was performed using *C wilfordii* extract, which was purchased at a local market as pure powder and prepared in our laboratory as described previously.⁴ A skin prick test result was negative; the intradermal test result was positive (mean wheal size 7.5 mm with 2 mg/mL of *C wilfordii*). The BAT was performed using flow cytometry (FACScantoII; BD Immunocytometry Systems, San Jose, California). Activated basophils were stained using allophycocyanin-conjugated anti-HLA-DR, fluorescein isothiocyanate-conjugated anti-CD123,

and phycoerythrin-conjugated anti-CD63 (BD Pharmingen, San Jose, California) triple labeling. For CD203c expression analysis, phycoerythrin-conjugated anti-CD203c (Beckman Coulter, Marseille, France) was used with the same allophycocyanin HLA-DR and fluorescein isothiocyanate CD123 markers. The patient's basophils were incubated with various concentrations of *C wilfordii* extract (0.02 – 2 mg/mL), anti-IgE antibody ($1 \mu\text{g/mL}$; Sigma Co, St Louis, Missouri) as a positive control, and without any extract as a negative control. To exclude nonspecific activation of basophils, 3 control individuals were included. The cells were gated initially based on the histogram defined by the forward and side scatters, and then a second gate of high fluorescein isothiocyanate CD123⁺ cells and low allophycocyanin HLA-DR was defined to select the basophil population, for an analysis of at least 500 basophils. The percentage of CD63–CD203c expression was defined as the percentage of basophils expressing more CD63–CD203c than the critical point located at $10^3 < x < 10^4$ on the histogram. This was determined by defining region M1 at histogram analysis. After incubation with the *C wilfordii* extract, the patient's basophils showed upregulation from 3.1% (spontaneous CD63 expression) to 27.7% for 2 mg/mL of *C wilfordii* extract (Fig 1A), whereas the CD63 expression in basophils from the 3 healthy controls remained unchanged ($<10\%$). For CD203c expression, a similar dose-dependent upregulation was seen (2.9% – 10.5% ; Fig 1B). The histogram data also are shown in Figure 1C and D.

She had no gastrointestinal symptoms after she stopped taking *C wilfordii*, and visual findings at follow-up esophagogastroscope were completely normal. In addition, repeated biopsy findings showed improved eosinophilic infiltrations (20 – 30 /high-power field).

This is the first reported case of EoE caused by *C wilfordii* usage and verified by BAT. We were able to diagnose EoE caused by *C wilfordii* using various lines of evidence. First, discontinuation followed by the rechallenge from her history suggested *C wilfordii* as the causative agent, which was the most important clue. Second, EoE was identified by typical findings at endoscopy and histology with improvement after discontinuation. Third, positive results from the intradermal test and BAT using *C wilfordii* extract showed the strongest evidence of immediate-type hypersensitivity caused by *C wilfordii*. The prevalence of EoE is increasing, but the cause and pathogenesis of EoE have not been identified clearly, and the cause has been difficult to detect.² Recently, thymic stromal lymphopoietin and basophils have been considered involved mainly in the pathogenesis of EoE, distinct from an IgE-dependent mechanism.^{5,6} Currently, BAT has proved sensitive and specific for the diagnosis of immediate allergic reactions, including inhalant allergens, food allergens, hymenoptera venom, and natural rubber latex allergy.^{7,8} However, there are few reports on cases of EoE using BAT. This case is meaningful because it was verified by BAT using *C wilfordii*

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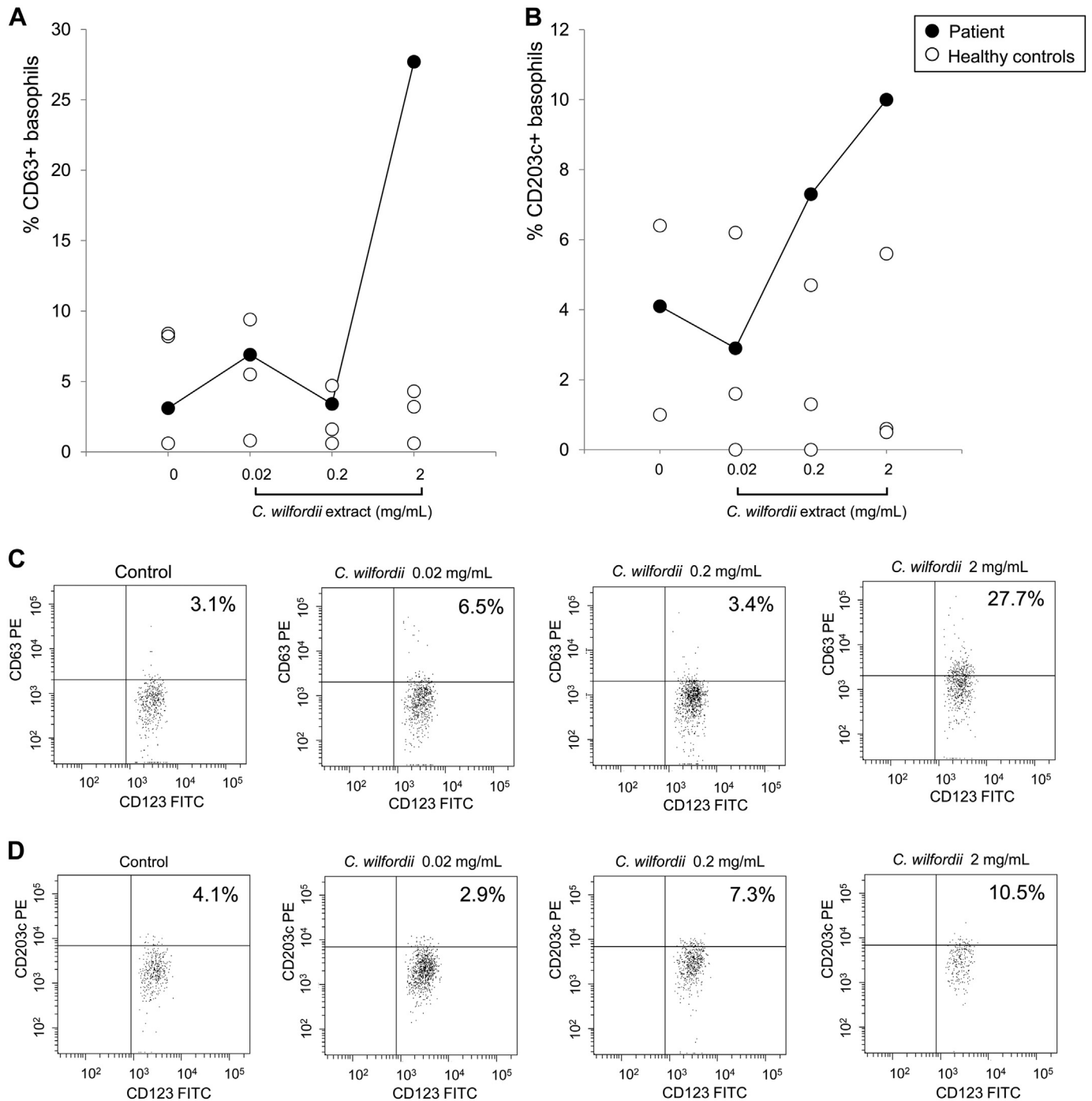


Figure 1. Expression of (A) CD63 and (B) CD203c in basophils after stimulation by *Cynanchum wilfordii* extract in the patient and 3 healthy controls. Flow cytometric data of the patient show (C) CD63 and (D) CD203c expression induced by *C. wilfordii* extract stimulation (0, 0.02, 0.2, and 2 mg/mL). FITC, fluorescein isothiocyanate; PE, phycoerythrin.

extract. We propose that BAT could be a useful additional cellular test, particularly for the diagnosis and identification of causative agents in EoE.

In conclusion, we report a case of eosinophilic esophagitis caused by repeated use of *C. wilfordii*, which was confirmed by history, endoscopic findings, histology, and BAT.

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References

- [1] Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol*. 2011;128:3–20.
- [2] Carr S, Watson W. Eosinophilic esophagitis. *Allergy Asthma Clin Immunol*. 2011;7:S8.
- [3] Chang A, Kwak BY, Yi K, et al. The effect of herbal extract (EstroG-100) on pre-, peri- and post-menopausal women: a randomized double-blind, placebo-controlled study. *Phytother Res*. 2012;26:510–516.
- [4] Hur GY, Park HJ, Kim HA, et al. Identification of Dioscorea batatas (sanyak) allergen as an inhalant and oral allergen. *J Korean Med Sci*. 2008;23:72–76.
- [5] Ray K. Oesophagus: TSLP–basophil axis important in eosinophilic oesophagitis. *Nat Rev Gastroenterol Hepatol*. 2013;10:502.
- [6] Siracusa MC, Kim BS, Spergel JM, et al. Basophils and allergic inflammation. *J Allergy Clin Immunol*. 2013;132:789–801.
- [7] Boumiza R, Debard AL, Monneret G. The basophil activation test by flow cytometry: recent developments in clinical studies, standardization and emerging perspectives. *Clin Mol Allergy*. 2005;3:9.
- [8] Sturm GJ, Kranzelbinder B, Sturm EM, et al. The basophil activation test in the diagnosis of allergy: technical issues and critical factors. *Allergy*. 2009;64:1319–1326.