

Clinical Notes

Erythema multiforme minor during sublingual immunotherapy

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Japanese cedar (JC) pollinosis is the most common allergy in Japan and is estimated to affect more than a quarter of the total Japanese population.¹ Allergen-specific immunotherapy is an established and effective method to reduce the symptoms of allergic disease by administering the antigen. For this reason, allergen-specific immunotherapy is expected to alter the natural course of allergic rhinitis and reduce the need for medication. Sublingual immunotherapy (SLIT) was also reported to have fewer severe side effects, and its efficacy and safety have been established.¹

Erythema multiforme (EM) is an acute, immune-mediated, mucocutaneous condition characterized by acraly distributed, distinct target lesions with concentric color variation.² It is associated with infection (e.g. herpes simplex virus and *Mycoplasma pneumoniae*), medications (e.g. non-steroidal anti-inflammatory drug, sulfonamides, antiepileptics, and antibiotics), malignancy, and autoimmune disease.² However, there are no reports of EM associated with SLIT. We report a case of erythema multiforme minor during sublingual immunotherapy. Informed consent was obtained from the parents for the publication of this case report.

A 14-year-old girl was given a sublingual drop of JC pollen (Cedartolen® 0.2 mL; 200 Japanese Allergy Units/mL/day) as SLIT. On the third day after administration she developed erythema with pruritus. On the fourth day, her symptoms aggravated and she developed fever; SLIT was therefore discontinued. She had JC pollinosis but no other allergic history, including atopic dermatitis, asthma, or food allergy. She was referred to our hospital on day 5, and we administered oral prednisolone at 20 mg/day but erythema, itching, and fever remained, and she was hospitalized on day 6. At the time of hospitalization, she had erythema with multiple small blisters on her back and abdomen covering more than 50% of the body surface area (Fig. 1a), excluding the mouth, and fever of 40.1 °C. Laboratory tests revealed slightly elevated C-reactive protein (1.79 mg/dL) and elevated antigen-specific IgE of JC

pollen (≥ 100 UA/mL), without other specific findings. Blood culture and IgM antibodies for measles, rubella, and mycoplasma were negative. We performed intravenous steroid pulse therapy (methylprednisolone at 1,000 mg/day for 3 days), and symptoms improved. Erythema was characterized by target lesions, which is characteristic of EM,² from the day after intravenous steroid administration (Fig. 1b). Pathological evaluation of abdominal skin revealed degenerative necrosis of the epidermis and edema, mainly of the dermal papillary layer (Fig. 1c). We reduced steroids, and she was discharged without recurrence of symptoms. The levels of thymus and activation-regulated chemokine (TARC), a useful prognostic biomarker of drug eruption,³ were elevated on day 5 (12,652 pg/mL) and relieved on day 18 (6,808 pg/mL). Moreover, lymphocyte stimulation test (LST) performed 1 month and 9 months later was positive (Fig. 1d). Mucosal lesions were not detected during the clinical course. Taken together, she was diagnosed with erythema multiforme minor.

In general, the safety and tolerability of allergen-specific immunotherapy have been established, and fatal adverse events are rare.⁴ Allergen-specific immunotherapy is usually performed through the subcutaneous or sublingual route and there is no difference in efficacy, although systemic reactions (e.g. cough, dyspnea, asthma, rhinoconjunctivitis, eczema, and anaphylaxis) are less common via the sublingual route.⁴ In a phase III study of SLIT, 13.5% of patients developed mild or moderate treatment-related adverse events, but none were severe.¹ One patient developed toxic eruption, which led to discontinuation.¹ Our patient was initially considered to have Stevens–Johnson syndrome or toxic epidermal necrolysis; however, she was finally diagnosed with EM minor because she had no mucosal lesions.⁵ A skin biopsy also supported the diagnosis of EM.² The LST aids in the diagnosis of drug hypersensitivity and drug allergy,⁵ which produced a positive result for Japanese cedar pollen extract in our case. Several limitations remain in this report. First, as the patient naturally had an allergy to JC pollen, the interpretation of elevated LST remains unclear. However, we considered that positive LST in the acute and convalescent phase might be meaningful as in drug-induced hypersensitivity syndrome. Finally, examinations of herpes simplex virus 6 and antinuclear antibodies were not

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Received 8 March 2020; revised 2 July 2020; accepted 28 July 2020.

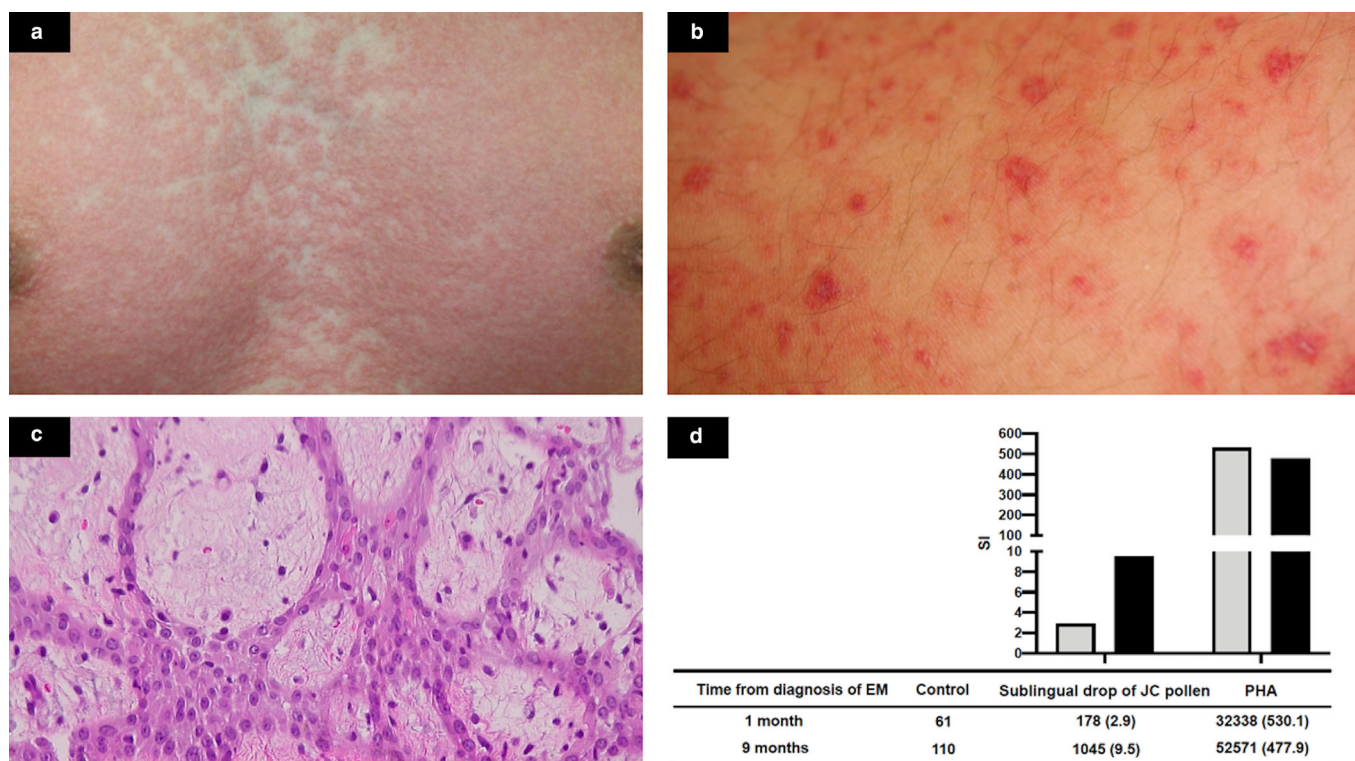


Fig. 1 (a) Erythema with multiple small blisters on the trunk of the body over more than 50% of the body surface area. (b) Erythema was characterized by target lesions, which is typical of EM. (c) Pathological evaluation revealed degenerative necrosis of epidermis, and edema, mainly of the dermal papillary layer. (d) The results of the lymphocyte stimulation test using the sublingual drop of Japanese cedar (JC) pollen at 1 month and 9 months from the diagnosis of EM. The amount of ^3H -thymidine incorporation is expressed as counts per minute (cpm), followed by the stimulation index (SI) in parentheses. The SI was calculated as the ratio of the stimulated-to-unstimulated sample. Phytohemagglutinin (PHA) was used as a positive control.

performed in our case, and it is difficult to deny other causes of EM.

Infection is the major cause of EM. In our case, we ruled out major infection by blood tests and pathological evaluation supported the diagnosis of EM. The median period to major adverse events in the phase III study of Cedartolen was within 2 weeks from administration,¹ and EM also developed within 2 weeks from the administration of the JC pollen drop in our case. Based on this clinical course it is difficult to exclude the possibility that EM was induced by the sublingual drop of JC pollen.

In conclusion, SLIT is an established treatment with good safety and tolerance. However, clinicians should be aware of the possibility of systemic adverse events.

Acknowledgments

The authors would like to thank Dr Toshiyuki Fukao, who amended the report. We also thank Dr Hitoshi Iwata and Dr Miki Nagai for their clinical support, and Dr Eiji Matsukuma for his academic support.

Disclosure

N.K. received lecture and chair fees from Torii Pharmaceutical Co., Ltd.

Author contributions

Y.M. designed and wrote the report. K.H. collected the patient's clinical data. K.M. and A.I. supervised the treatment for the patient. N.K. mainly reviewed and amended the manuscript. All authors gave their final approval for the version to be submitted.

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