

## Two cases of eczematous drug eruption caused by oral tacrolimus administration

Ryuichi Saito, Yu Sawada  and Motonobu Nakamura

*Department of Dermatology, University of Occupational and Environmental Health, Kitakyushu 807-8555, Japan*

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*Correspondence:* Yu Sawada, Department of Dermatology, University of Occupational and Environmental Health, 1-1 Iseigaoka, Yahatanishi-ku, Kitakyushu 807-8555, Japan. Tel: +81 93 691 7445; Fax: +81 93 691 0907. E-mail: long-ago@med.uoeh-u.ac.jp

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Tacrolimus is a immunosuppressive agent widely used for the treatment of autoimmune diseases and in transplant recipients (1). In view of its pharmacological effect, it is assumed that tacrolimus-induced cutaneous adverse events are relatively rare. Herein, we report the first 2 cases of an eczematous drug eruption caused by systemic tacrolimus administration in the English-language literature.

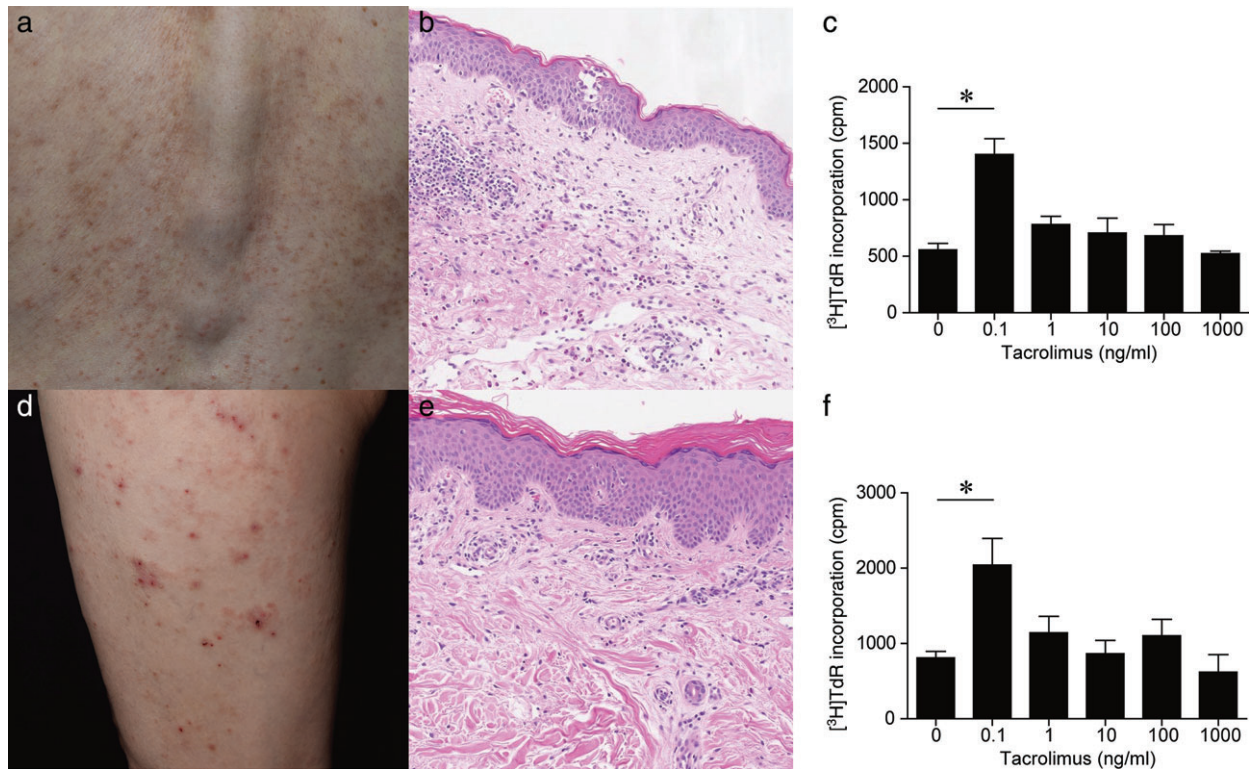


**Fig. 1.** Clinical manifestations and laboratory examinations. (a) Clinical picture, first case: scaly erythematous papules on the trunk. (b) Histological specimen of case 1: lymphocytes and eosinophils infiltrated into the dermis, and epidermal vesicle. (c) Lymphocyte stimulation test (LST) of case 1. The patient's peripheral blood mononuclear cells ( $2 \times 10^5$ /well) taken at the initial visit were cultured for 72 h in a 96-well plate with tacrolimus, and the proliferative responses were assessed by  $^3\text{H}$ -thymidine ( $^3\text{H}$ -TdR) incorporation. The results are presented as the mean  $\pm$  standard error of the mean (SEM). The  $p$ -value was obtained with Student's  $t$ -test. (d) Clinical picture of the second case: scaly erythematous papules and plaques on the thigh. (e) Biopsy of case 2: lymphocytes infiltrated into the epidermis. (f) LST of case 2. The results are presented as the mean  $\pm$  SEM. The  $p$ -value was obtained with Student's  $t$ -test.

## Case Report

The first case was a 59-year-old female receiving tacrolimus for rheumatoid arthritis. One month after drug administration, she noticed eczematous, pruritic papules and erythema on her trunk and extremities (Fig. 1a). She took no other immunosuppressive agents. A skin biopsy showed infiltration of lymphocytes and eosinophils in the dermis with epidermal spongiosis and vesicles (Fig. 1b). To investigate the causative drug, we performed a lymphocyte stimulation test (LST) as previously described (2), and found a positive reaction at 0.1 ng/ml (Fig. 1c). To exclude a false-positive LST result with tacrolimus at 0.1 ng/ml, we performed control LSTs in patients exposed to tacrolimus without cutaneous adverse events ( $n = 3$ ) and healthy subjects ( $n = 3$ ) (Figure S1). Patch testing with tacrolimus 1%, 2%, 10% and 20% pet. gave negative results on day (D) 2 and D7. Therefore, we diagnosed the patient's skin eruption as a

tacrolimus-induced drug eruption resembling eczema. After topical application of betamethasone butyrate propionate ointment and the discontinuation of the drug, her skin eruption improved within 1 week.

The second case was a 58-year-old female who had been treated for rheumatoid arthritis for 13 years with various biological agents such as etanercept. After these treatments, her arthritis improved, and tacrolimus was started. Nine years after she had starting taking tacrolimus, she noticed scaly erythematous papules (Fig. 1d). We first treated her skin eruption as eczema; however, topical betamethasone butyrate propionate ointment did not improve her skin eruption. To investigate the cause of her skin eruption, we performed a skin biopsy, which revealed infiltration of lymphocytes into the epidermis and dermis (Fig. 1e). Eosinophils were also observed in the dermis. Therefore, we considered the patient's skin eruption to be possibly a drug eruption

caused by tacrolimus. An LST showed a positive reaction at 0.1 ng/ml (Fig. 1f). We could not obtain consent for patch testing from this patient. In conclusion, we diagnosed an eczematous drug eruption caused by tacrolimus. After topical application of betamethasone butyrate propionate ointment and the discontinuation of tacrolimus, her skin eruption improved remarkably within 2 weeks.

## Discussion

Although several cases of allergic contact dermatitis caused by topical tacrolimus in atopic dermatitis patients have been reported, our cases are the first cases following systemic tacrolimus treatment reported in the English-language literature. There are, altogether, 6 cases of tacrolimus-induced drug eruption (Table S1) (3–6): 2 cases of allergic contact dermatitis, 1 case of Stevens–Johnson syndrome, 1 maculopapular drug eruption, and 2 cases of eczematous drug eruption. Furthermore, the causative drug was diagnosed by LSTs in all cases except the case of allergic contact dermatitis. As, mostly, only molecules with a molecular weight (MW) of <500 pass through the epidermis, it might be difficult for tacrolimus, with a MW of 822, to penetrate normal skin. Only 1 case of allergic contact dermatitis showed a positive patch test result; the outcome might depend

on the skin condition. Moreover, it might depend on the difference in the concentrations of tacrolimus that are necessary for eliciting an allergic reaction versus exerting its own immunosuppressive effect (1). Regarding the LST, it should be kept in mind that the drug concentration might be a key factor in diagnosing the causative drug, including immunosuppressive agents.

## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Figure S1.** LST using tacrolimus in control subjects. Peripheral blood mononuclear cells were taken from patients exposed to tacrolimus without cutaneous adverse events ( $n = 3$ ) and healthy subjects ( $n = 3$ ), and  $2 \times 10^5$  cells/well were cultured for 72 h in a 96-well plate with or without tacrolimus at a concentration of 0.1 ng/ml, and the proliferative responses were assessed by  $^3\text{H}$ -TdR incorporation. Results are presented as the mean  $\pm$  SEM.  $p$ -Value was obtained with Student's  $t$ -test.

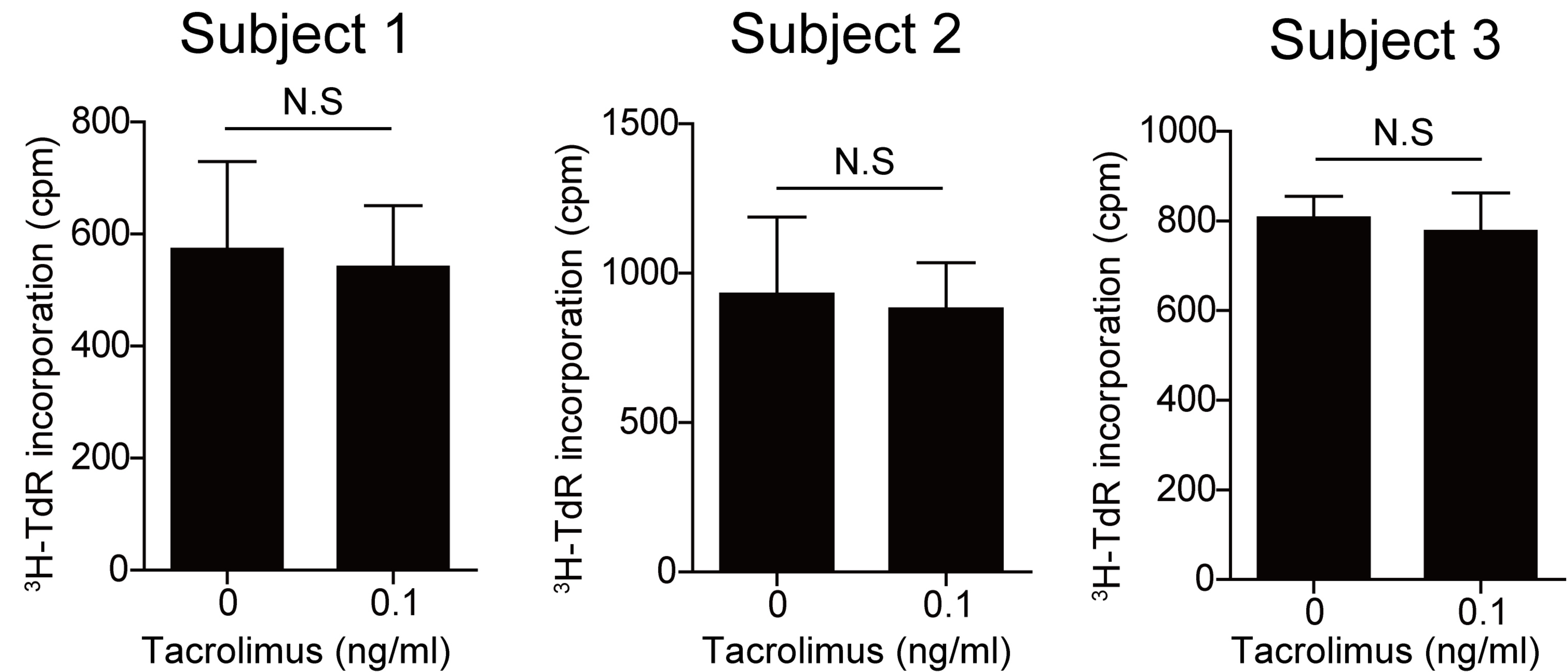
**Table S1.** Reported cases of drug eruption caused by tacrolimus.

## References

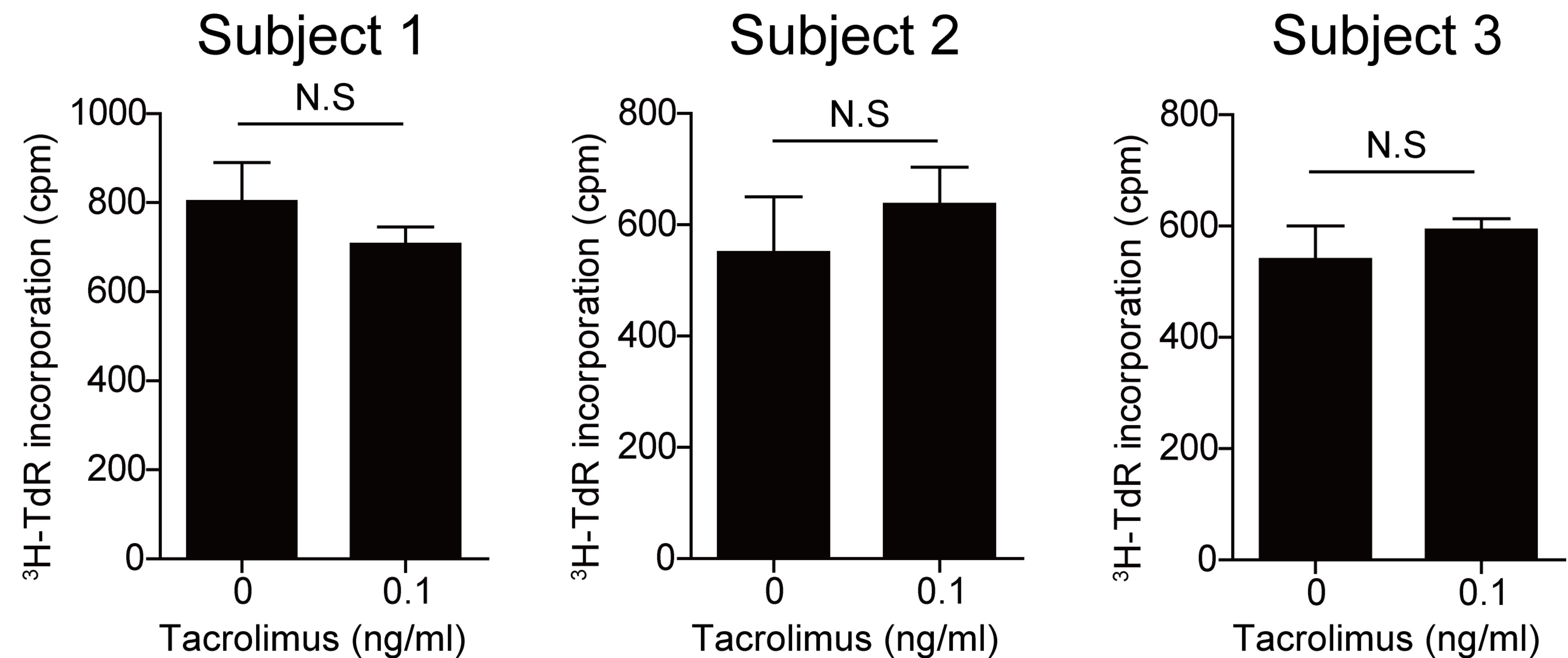
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Supplementary figure 1

Healthy subject



Control patients exposed to tacrolimus without cutaneous side effect



| Supplementary Table S1. Reported cases of drug eruption caused by tacrolimus |     |        |                             |            |                             |
|------------------------------------------------------------------------------|-----|--------|-----------------------------|------------|-----------------------------|
| Author                                                                       | Sex | Age    | Eruption type               | Interval   | Test for causative drug     |
| Shaw DW, et al [3]<br>Schmutz JL, et al [4]                                  | 9   | Male   | Allergic contact dermatitis | 8 months   | Patch test                  |
| Yamanaka T, et al [5]                                                        | 54  | Male   | Stevens-Johnson syndrome    | 20 months  | Lymphocyte stimulation test |
| Yoshida H, et al [6]                                                         | 50  | Male   | Maculopapular type          | 3 months   | Lymphocyte stimulation test |
| Our case                                                                     | 59  | Female | Eczematous type             | 1 months   | Lymphocyte stimulation test |
| Our case                                                                     | 58  | Female | Eczematous type             | 108 months | Lymphocyte stimulation test |