

Photosensitivity with eosinophilia due to ambroxol and UVB

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Ambroxol stimulates synthesis and secretion of surfactant by pneumocytes and inhibits sodium absorption by airway epithelial cells (1). Although ambroxol is widely used for respiratory diseases, photosensitivity due to ambroxol has not been reported in the English language literature. In general, the action spectrum of drug-induced photosensitivity is in the ultraviolet (UV)A range (2). We report a case of UVB photosensitivity due to oral ambroxol.

Case Report

An 82-year-old Japanese male farmer presented with a 10-day history of erythema on sun-exposed areas. For 2 years, he had taken atenolol and amlodipine for hypertension. He visited his general physician for upper respiratory inflammation on January 28 and was given lysozyme, clofedanol, clarithromycin, cetirizine, and ambroxol. He worked outside on February 5 and developed a pruritic eruption on his face on February 7. The eruption rapidly spread to the dorsum of both hands, accompanied by severe oedema. He was treated with systemic steroids for 3 days but did not markedly improve.

On presentation, he had a pruritic, oedematous, scaly erythema on his face and 'V' area of his neck (Fig. 1a) and a papulosquamous eruption on the dorsum of his hands (Fig. 1b). There was clear sparing of the fingers webs.

He had an eosinophilia ($1300/\text{mm}^3$) and slightly elevated liver function tests. Serum zinc, niacin, coproporphyrin, and urinary uroporphyrin were all within normal limits. A drug-induced lymphocyte stimulation test (3) for ambroxol was negative.

Histology of a skin biopsy taken from the dorsum of his hand showed slight spongiosis in the epidermis and perivascular infiltration of lymphocytes in the upper dermis (Fig. 2). There was no deposit positive for periodic acid-Schiff stain.

We performed a screening phototest on his back on his first visit, using a DERMARAY type 320 (Clinical Supply Co., Gifu, Japan) equipped with Toshiba fluorescent lamps: FL32SBL/DMR for UVA and FL32SE-30/DMR for UVB. A 5-mm-thick glass filter was inserted during UVA lamp irradiation to eliminate UVB. The phototest was performed with three doses of exposure (5, 10, and 15 J/cm^2) for UVA and six doses of exposure (10, 20, 30, 60, 90, and 120 mJ/cm^2) for UVB. For Japanese, the minimal erythema dose (MED) of UVA is usually over 15 J/cm^2 and the MED of UVB is between 60 and 120 mJ/cm^2 . When evaluated 2 D after the phototest, 15 J/cm^2 of

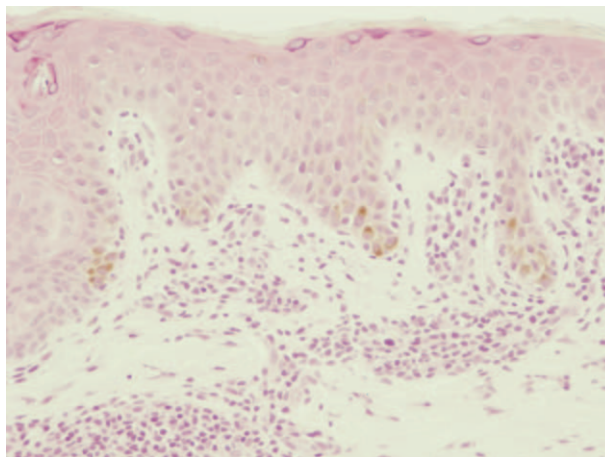


Fig. 2. Slight spongiosis in epidermis and perivascular infiltration of lymphocytes in the upper dermis (haematoxylin and eosin, original magnification $\times 200$).

UVA irradiation induced no reaction, but the patient's MED of UVB was below 10 mJ/cm^2 . The UVB phototest at 10 mJ/cm^2 provoked an indurated, papular, severe erythema (Fig. 3a). A biopsy from the test area showed epidermal severe spongiosis and perivascular dense infiltration of lymphocytes and eosinophils (Fig. 3b). Immunohistochemical examination showed CD4-positive cells mainly in the upper dermis and CD8-positive cells mainly in the epidermis.

His oral medicines were stopped. With topical corticosteroid therapy and protection of sun exposure, the eruption gradually improved and the eosinophilia resolved. The eruption had completely resolved after 4 weeks,

all topical drugs were then stopped, and the phototests were repeated. These tests were now within the normal range, i.e. the MED of UVA was over 15 J/cm^2 , the MED of UVB was 90 mJ/cm^2 , and 90– 120 mJ/cm^2 of UVB irradiation induced only erythema.

Patch tests and photopatch tests were carried out with baseline allergens (patch tester TORII; Torii Co, Tokyo, Japan) and the patient's oral medicines (10% in pet.) using 5 J/cm^2 of UVA irradiation. The patch test with 10% of ambroxol produced an indurated erythema, but the tests with other drugs showed no reaction. UVA irradiation did not enhance the reaction to ambroxol or induce any reaction on the patch test sites of the other drugs. We then performed patch tests using five different concentrations (from 10% to 0.05%) of ambroxol. The lower concentrations of ambroxol induced weaker reactions, but even 0.05% of ambroxol induced slight erythema. Photopatch testing using 0.05% of ambroxol followed by irradiation with 5 J/cm^2 of UVA or 15 mJ/cm^2 of UVB was then performed. Although UVA did not enhance the patch test, UVB caused an indurated erythema at the patch test site (Fig. 4).

Next, we performed an oral photo-challenge test with the normal dose (45 mg) of ambroxol for 3 days, followed by UV irradiation with the same range of doses used in the initial phototests. Oral photo-challenge test was negative for UVA, and the MED of UVB was 90 mJ/cm^2 . But, 120 mJ/cm^2 of UVB irradiation caused an

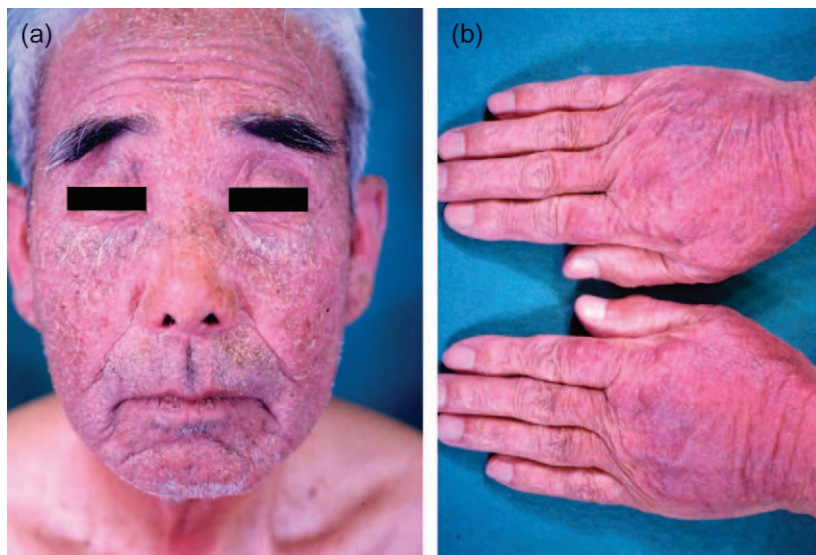


Fig. 1. Pruritic oedematous scaly erythema on the face (a), and papulosquamous eruptions on the dorsum of hands (b).

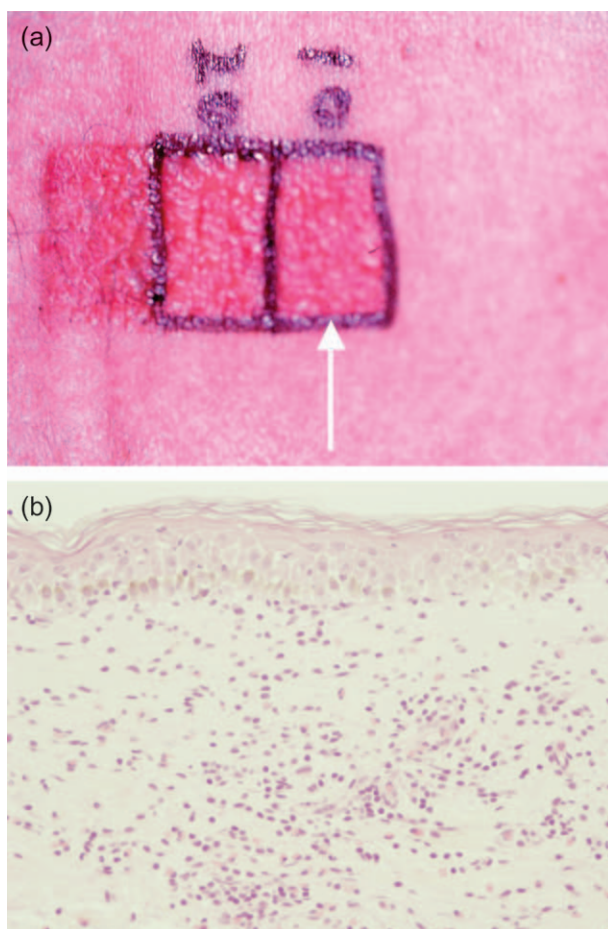


Fig. 3. (a) The ultraviolet B phototest at 10 mJ/cm^2 provoked indurated, papular erythema (white arrow). (b) Epidermal severe spongiosis and perivascular dense infiltration of lymphocytes and eosinophils (haematoxylin and eosin, original magnification $\times 200$).

indurated erythema 2 D after the oral photo-challenge test. Histology of this test site showed histological changes

similar to the patient's lesions at the first visit. An eosinophilia did not develop with oral photo-challenge test.

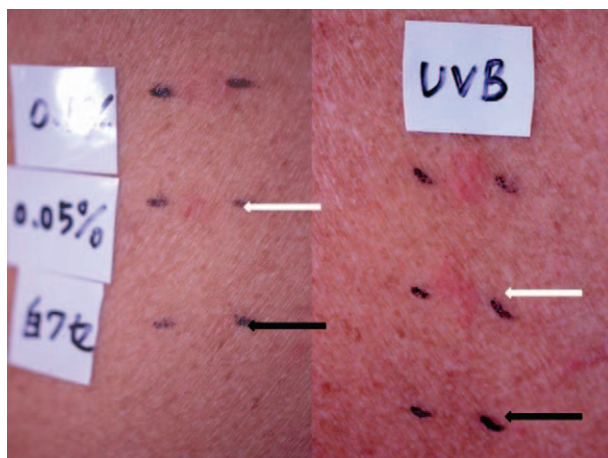


Fig. 4. Photopatch test of 0.05% of ambroxol presented indurated erythema with ultraviolet (UV)B irradiation (white arrow, right side) and only erythema without UVB irradiation (white arrow, left side). Pet. only with (black arrow, right side) and without UVB irradiation (black arrow, left side).

Discussion

We describe a case of UVB photosensitivity due to ambroxol confirmed by (i) the eruption was localized to sun-exposed areas and improved with cessation of oral medicines and sun protection; (ii) our patient represented with a pruritic papulosquamous rash suggesting an eczematous reaction; (iii) histological changes from both the initial eruption and the phototest site showed the same eczematous reactions; (iv) the initial phototest showed abnormal reaction to UVB, but the photosensitivity became normal after the eruption cleared; (v) photopatch tests for all drugs with UVA irradiation were negative, while UVB irradiation enhanced the response of patch testing to ambroxol; (vi) oral photo-challenge test with ambroxol produced a negative reaction to UVA and an abnormal MED of UVB ($\times 1.3$ normal).

Although ambroxol (Fig. 5) is widely used for upper respiratory disease, photosensitivity due to ambroxol is rare and only one case has been reported in the Japanese literature (4), in which the patient was also sensitive to UVB. Drug-induced photosensitivity is usually induced by UVA (2) and UVB photosensitivity due to a drug is rare (5–9). Although the exact mechanism by which our patient showed hypersensitivity to the UVB range is not clear, we consider that it is partly because the absorption spectrum of ambroxol hydrochloride in an aqueous solution peaks at 243–247 nm and 306–310 nm (4).

Two remarkable findings were observed in our case. First, UVB aggravated patch testing with 0.05% ambroxol. Auffret et al. (10) reported a similar phenomenon in a 36-year-old female who showed UVB photosensitivity to isotretinoin. Their patient showed erythema at the patch test site with 0.001% isotretinoin, and UVB irradiation aggravated the patch test reaction. The possible mechanism for this phenomenon, however, is not mentioned in their

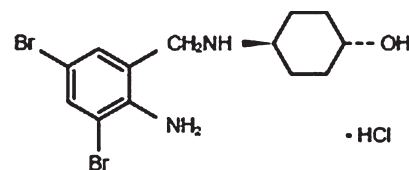


Fig. 5. The structure of ambroxol hydrochloride.

report. Second, eosinophilia was observed and, moreover, a biopsy specimen from the initial UVB phototest area showed a dense perivascular eosinophilic infiltration, which regressed after cessation of oral medicines and the use of topical corticosteroids. The patient in the previous report (10) also showed a peripheral eosinophilia, but no reports have ever mentioned the relationship between eosinophilia and drug-induced photosensitivity.

In summary, we report a rare case of photosensitivity due to ambroxol and UVB. Remarkable findings were the UVB aggravation of patch tests to the drug and that eosinophilia was associated with the photosensitivity.

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References

1. Gillissen A, Nowak D. Characterization of N-acetylcysteine and ambroxol in anti-oxidant therapy. *Respir Med* 1998; 92: 609–623.
2. Gonzalez E, Gonzalez S. Drug photosensitivity, idiopathic photodermatitis, and sunscreen. *J Am Acad Dermatol* 1996; 35: 871–887.
3. Mori H, Yamanaka K, Kaketa M et al. Drug eruption caused by azathioprine: value of using the drug-induced lymphocytes stimulation test for diagnosis. *J Dermatol* 2004; 31: 731–736.
4. Hazano S, Isonokami M, Higashi N. Photosensitivity due to ambroxol. *Pract Dermatol* 1992; 14: 53–56. (article in Japanese).
5. Emmet E A. Diphenhydramine photoallergy. *Arch Dermatol* 1974; 110: 249–252.
6. Torinuki W. Photosensitivity due to hydrochlorothiazide. *J Dermatol* 1980; 7: 293–296.
7. Frain-Bell W. A study of persistent photosensitivity as a sequel of the prior administration of the drug benoxaprofen. *Br J Dermatol* 1989; 121: 551–562.
8. Zenarola P, Gatta S, Lomuto M. Photodermatitis due to nifedipine: Reports of 2 cases. *Dermatologica* 1991; 182: 196–198.
9. Kondo S, Kagaya M, Yamada Y et al. UVB photosensitivity due to ranitidine. *Dermatology* 2000; 201: 171–173.
10. Auffret N, Bruley C, Brunetiere R A et al. Photoaggravated allergic reaction to isotretinoin. *J Am Acad Dermatol* 1990; 23: 321–322.

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