Valsartan-induced Drug Eruption Followed by CD30+ Pseudolymphomatous Eruption

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Accepted May 18, 2009.

Although the causes of CD30+ pseudolymphoma are unclear in most cases, drugs are one of the causative agents for this skin eruption, as represented by amlodipine (1), carbamazepine (2) and other drugs. Here, we report a patient with a maculopapular drug eruption to valsartan, an angiotensin II receptor 1 antagonist, which was followed by the development of CD30+ pseudolymphomatous lesions.

CASE REPORT

An 80-year-old Japanese man presented with a generalized maculopapular eruption. Two months previously he had begun taking valsartan (40 mg daily) for his hypertension. Two weeks after administration of the drug, he developed a rash on the trunk and all four limbs. The patient was seen by a private dermatologist and was administrated with an antihistamine with no therapeutic effect. He was referred to us for evaluation of his eruption.

On examination, multiple, pruritic, erythematous macules and papules were present on his chest, back and extremities (Fig. 1A and B). Laboratory examination revealed that leukocyte count was 7100/μl with eosinophilia (1590/μl, 22.4%; normal, 1–5%). There were no circulating atypical lymphocytes. Biochemical profiles showed renal dysfunction with high values of serum creatinine, 1.46 mg/dl (normal, 0.6–1.1 mg/dl); blood urea nitrogen, 26 mg/dl (normal, 8–22 mg/dl); and hyperkalaemia, 5.1 mEq/l (normal, 3.6–4.9 mEq/l). Other values, including hepatic enzymes, were within normal ranges. A skin biopsy specimen taken from his abdomen revealed an infiltrate of lymphocytes in the upper dermis, intermingled with eosinophils (Fig. 2A). We performed immunohistochemistry of this biopsy, but CD30+ cells were not seen. We performed lymphocyte stimulation test with valsartan, as reported previously (1, 2), and found that 3H-thymidine incorporation was significantly increased by ≥5 ng/ml of the drug. Based on the clinical course and lymphocyte stimulation test, we diagnosed the rash as drug eruption due to valsartan.

The intake of valsartan was discontinued, and he was treated with oral prednisolone (30 mg daily) and topical betamethasone butyrate propionate ointment. The maculopapules were remarkably improved in a week, and prednisolone was tapered over the next 2 weeks. During the next 4 months residual faint erythematous papules occurred on the back (C) and legs (D).

Fig. 1. Clinical features. At the initial eruption, diagnosed as toxicoderma, multiple, pruritic, erythematous macules and papules were present on his chest (A) and back (B). At the subsequent eruption, diagnosed as pseudolymphoma, erythematous solid papules occurred on the back (C) and legs (D).
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macules continued at a low level. However, a general-
ized but different type of eruption re-emerged on his
abdomen, back, and extremities (Fig. 1C and D). The
individual papular lesions were more solid than those
of the previous eruption. A skin biopsy specimen taken
from a papular lesion revealed a massive infiltrate of
lymphocytes, some of which had large nuclei with pro-
minent nucleoli in the upper and middle dermis (Fig.
2B). The infiltrate was intermingled with eosinophils.
An immunohistochemical study demonstrated that
CD4+ cells outnumbered CD8+ cells, and notably, large
atypical cells expressed CD30 (Fig. 2C). We diagnosed
the eruption as CD30+ pseudolymphoma, following
valsartan drug eruption, or as lymphomatoid papulosis.
The patient was treated with narrowband ultraviolet
B light irradiation (800 mJ/cm², once a week for 14
weeks) without re-administration of prednisolone. The
eruption subsided gradually in 4 weeks. Currently, 2
months after the cessation of therapy, no skin lesions
have recurred.

DISCUSSION

The well-known adverse effects of valsartan are dizzy-
ness, abdominal pain and cough. The cutaneous reac-
tions are less frequent, but urticaria or angioedema (3)
and mucocutaneous bullous pemphigoid (4) have been
reported. In our patient, a maculopapular eruption ini-
tially occurred in response to valsartan. This common
type of drug eruption was improved by discontinuation
of the causative drug and administration of prednisolo-
one. After a 4-month remission of the eruption, however,
he developed an eruption, which was different from the
antecedent rash. The newly developed eruption had
solid papular appearance and histological presence of
CD30+ large atypical cells. Lymphomatoid papulosis
may be a differential diagnosis, but the eruption did not
recur after the successful treatment with narrowband
UVB therapy. Pseudolymphoma is one of the mani-
festations of drug eruptions (1, 2, 5). There have been
several reports of CD30+ pseudolymphoma caused
by drugs (1, 2). Only one case of valsartan-induced
pseudolymphoma was documented, although CD30
positivity was not examined (6).

The relationship between the initial drug eruption
and the subsequent pseudolymphomatous eruption is
unclear in our case. However, considering the presence
of preceding drug eruption and the apparent reactivity
of patient’s peripheral lymphocytes to valsartan stron-
gly suggests that the pseudolymphomatous eruption
developed as a consequence of sensitization with the
drug and subsequent hyper-reaction with the drug. It
is tempting to speculate that valsartan-reactive T cells
were overstimulated during the clinical course and
led to the pseudolymphoma after a long incubation
period.

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