

## Fixed Drug Eruption due to Cimetidine

Sir,

Cimetidine, the first antagonist of the H<sub>2</sub> receptors, has been used extensively with infrequent side-effects. There have been several reports of pruritus, exanthema, urticaria, erythema multiforme (EM) and dermatitis associated with this drug (1). We present a case of fixed drug eruption due to cimetidine which, to the best of our knowledge, has not previously been reported in the literature.

### CASE REPORT

A 58-year-old Japanese woman presented with pruritic and tender erythematous plaques on her back, both shoulders and rightdorsal hand 3 h after she had taken cimetidine and other medications for gastric ulcer. She was occasionally treated with 600 mg of cimetidine three times daily. The patient had had three identical episodes with skin lesions localized to the same sites following the ingestion of medication for gastric ulcer. She reported that she had a history of allergy to chlormezanone.

Physical examination showed multiple erythematous plaques, varying from 1.0 cm to 10.0 cm in diameter, on her back, shoulder and rightdorsal hand. Within a week, the eruptions on her back and shoulder faded with no residual pigmentation. Two days later, a large erythematous plaque on the dorsal hand developed a central flaccid bulla followed by pigmentation. Notable laboratory values were as follows: an increased IgG concentration at 1.969 mg/dl and a decreased IgM concentration at 87 mg/dl.

Histological examination of early stage lesions 4 h after cimetidine challenge showed a normal epidermis, oedema of the papillary dermis and perivascular inflammatory cell infiltration, predominantly consisting of neutrophils. There was no hydrophic degeneration of the basal layer, but epidermal melanocyte incontinence was present on the biopsy specimen from the right dorsal hand with residual hyperpigmentation. Immunohistological studies were performed. Direct immunofluorescence was entirely negative. Then, HLA-DR was intermediately expressed on the surface of keratinocytes and dermal endothelial cells. Expression of intercellular adhesion molecule-1 (ICAM-1) by keratinocytes was weakly present in the basal layer.

Patch testing of quiescent sites and normal skin using cimetidine showed no reaction. However, an oral challenge test with cimetidine provoked a positive reaction, and new large macules were noticed on the patient's lower leg and lower lip. Subsequent separate challenges with three other medications produced negative results. There was no cross-reaction with ranitidine or famotidine.

### DISCUSSION

Histologically suggesting that fixed drug eruption is a variant of EM, fixed drug eruption could be considered as within the "EM spectrum" (2). Although there is disagreement whether EM, Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN) are variants within a continuous "EM spectrum", bullous

fixed lesions could become more numerous and more severe, eventually resembling TEN. In our patient, a gradual spread occurred with successive oral challenge test.

The non-pigmenting form of fixed drug eruption has been described as a second type of fixed drug eruption (3). In our patient, two plaques on both shoulders and several macules on her back were not followed by pigmentation. We considered these lesions to be the non-pigmenting type of fixed drug eruption. However, the lesion on the right dorsal hand followed by residual pigmentation was the classical type. The patient presented two different clinical forms of fixed drug eruption at the same time. The intensity of the inflammatory response was proportionate to the degree of pigmentation. Non-pigmenting fixed lesions may become pigmented with repeated exposure. The sites of predilection of pigmented fixed drug eruptions might be predetermined by local injury and/or anatomical conditions. The mechanism leading to fixed drug eruptions remains unknown. We suggest that the pathogenetic mechanism of fixed drug eruptions could vary with the causative agent. In this case, at the early stage of fixed drug eruption we observed histologically neutrophilic infiltration, not lymphocytes and HLA-DR expression, not ICAM-1, although the typical histopathological features of fixed drug eruption lesions suggest that a lymphocyte-mediated attack on epidermal cells is a primary event and it is reported that the intensity of expression of ICAM-1 by keratinocytes correlates well with the degree of epidermal invasion of lymphocytes in fixed drug eruption lesions (4).

### REFERENCES

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