Minocycline-induced Acute Generalized Exanthematous Pustulosis in a Patient with Generalized Pustular Psoriasis Showing Elevated Level of sELAM-1

Sir,

We here describe a case of acute generalized exanthematous pustulosis (AGEP) by minocycline in a patient with generalized pustular psoriasis (GPP), well controlled by etretinate.

A 52-year-old female with GPP was being followed-up as an outpatient. Eight years previously, generalized pustulation with arthralgia of her shoulders and lumbago had occurred following a throat infection, which later developed into erythroderma. After admission, her lesions improved after treatment with etretinate (40 mg/day), which proved to be an effective therapy, and the symptoms gradually subsided. She then complained of a sicca condition and was examined by Shirmer test (*r*; 3 mm, *l*; 4 mm), gum test (8 ml/10 min) and lip biopsy (grade III), which demonstrated the presence of Sjögren's syndrome. Keratoconjunctivitis sicca was not noted. Antinuclear antibody was positive at a titer of 1 : 80 (speckled), but rheumatoid factor, anti-RNP, anti-SS-A and SS-B antibodies were all negative. Afterwards her GPP was well controlled with etretinate 10 mg/day. However, in July 1995, she developed several folliculitis-like papules limited to the perioral area, and minocycline (100 mg/day) was administered. Three hours after the patient had taken minocycline, erythroderma with numerous superficial pustules developed over her body (Fig. 1) and she developed a fever of 39°C. Culture of the pustule was sterile. She stated that similar systemic pustulation had occurred 5 years previously, and old clinical records also revealed that minocycline, which had been administered for folliculitis (200 mg/day), had induced generalized pustulation on the 7th day of administration. Laboratory examination revealed normal blood cell counts, deviating serum GOT, GPT, LDH, γ-GTP, Al-P, T-Bil levels, an elevated erythrocyte sedimentation rate, and positive C-reactive protein. A drug lymphocyte stimulation test was positive (stimulation index; 465%). Serum cytokine levels of interleukin-2 (IL-2), IL-6, IL-8, tumor necrosis factor-α (TNF-α), and endothelial-leukocyte adhesion molecule-1 (ELAM-1) were measured by radioimmunoassay (IL-2, Amersham) and ELISA (IL-6, Fuji; IL-8, Toray; TNF-α, Otsuka; ELAM-1, R&D). As shown in Table I, on the 3rd day from onset, IL-6 was 22.9 pg/ml (normal, 10 pg/ml), IL-8 was 19.2 pg/ml (normal <10 pg/ml), and ELAM-1 demonstrated 400 ng/ml (normal, 29.1–63.4 ng/ml); however, IL-2 and TNF-α were both within normal ranges. After the minocycline treatment had been stopped, spontaneous rapid resolution of the pustules was observed within 10 days. The elevated liver enzyme levels then decreased gradually. A patch test of 10% minocycline, which was performed on the patient's back after remission, showed pustules (the vehicle was negative and 10% minocycline was also negative in the normal controls). After 18 days, the serum cytokine levels examined had all decreased to the normal ranges. The patient remained on etretinate 10 mg/day throughout the course.

Table I. *Serum concentrations of various cytokines after the onset of systemic pustulation*

	IL-2 (U/ml)	IL-6 (pg/ml)	IL-8 (pg/ml)	TNF-α (pg/ml)	ELAM-1 (ng/ml)
July 4	<0.8	22.9	19.2	<5.0	400
July 18	<0.8	<10	<10	<5.0	60.2

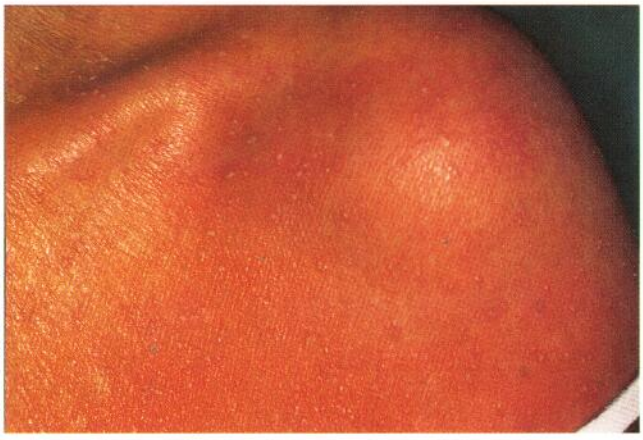

Fig. 1. Pustular small eruptions on an erythroderma background.

Drug-induced GPP is a well-described phenomenon, and numerous case reports implicating drug exposure to be the cause of GPP have been published. Recently, a few cases with a severe hypersensitivity reaction developing into pustulation have been reported to be caused by minocycline (1). However, to our knowledge, minocyline has not previously been reported to induce GPP. Tsankov et al. (2) advocate that tetracyclines should be avoided in patients with psoriasis, because they can occasionally exacerbate psoriasis. Our case demonstrated that minocycline caused well-controlled GPP to develop into AGEP. One reason may be that our patient also had the complication of Sjögren's syndrome, which occasionally develops drug eruptions (3). AGEP usually occurs following either drug ingestion or viral infection (4). A few cases of AGEP induced by cyclines have been previously reported (4, 5). In our case, positive DLST test, patch test and accidental rechallenge test all confirmed minocycline to be the causative drug for the generalized pustular eruptions. Spontaneous rapid resolution within 10 days, with transient elevated serum liver enzyme levels, indicated that the symptoms were due to AGEP in a patient with GPP, and not an exacerbation of GPP. Recently, Spencer et al. (6) observed generalized pustular eruption after drug administration. They believe pustular drug eruption to be a distinct entity, different from GPP. The absence of any personal or family history of psoriasis, the spontaneous resolution without therapy, the presence of eosinophils in the inflammatory infiltrates and the absence of any histological features of conventional psoriasis all suggest pustular drug eruptions to represent a distinct entity.

In our case, the serum cytokine levels of IL-6 and IL-8 were also elevated. IL-8 strongly attracts both neutrophils and lymphocytes. Furthermore, it is of note that a markedly elevated level of serum ELAM-1 was demonstrated at the beginning of systemic pustulation, which thereafter decreased rapidly in parallel with the clinical improvement in this case. ELAM-1 is thought to mediate the adherence of neutrophils

to endothelial cells and thus accounts for the migration of the cells from the blood-stream to the epidermis, which may have played a crucial role in the formation of pustulation in our case. Sagawa et al. (7) reported that an elevated serum level of TNF-α is maintained in the pustular stage, which explains such clinical symptoms in GPP as fever and leukocytosis. TNF-α induces endothelial cells to express ELAM-1 (8). In our case, however, TNF-α was observed within the normal range. The reason for this discrepancy, however, is unknown. Recently, an elevated level of circulating ELAM-1 has been reported in erythrodermic skin diseases, including psoriasis (9). The significantly high level of serum ELAM-1 detected in our case may have been due to erythrodermic condition.

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