Adverse Reaction to Methotrexate and Etretinate in a Patient with Psoriasis

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A 49-year-old Caucasian male patient suffered from fever, general weakness and diffuse hair loss on the scalp for 3 days. Skin lesions showed erythematous scaly patches with pustules and erosions on the lower extremities and perianal region, and multiple ulcerations on the labial mucosa. A complete blood cell count revealed thrombocytopenia and leukopenia, which gradually worsened day after day (platelet: 29,000/mm³, WBC: 1.000/mm³). Candida albicans was isolated from the lesions of the oral cavity and lower extremities.

Twelve days prior to the visit, he had taken etretinate (Tegison®) PO. 25mg/day, prednisolone PO. 50mg/dy and methotrexate PO. 15mg/day for 5 days for the treatment of psoriasis.

We presume that these adverse reactions may be synergistic adverse reactions, probably due to methotrexate and etretinate in consideration of the patient's history. (Ann Dermatol 1:59—63, 1989)

Key Words: Adverse reaction, Etretinate, Methotrexate, Psoriasis

Methotrexate (MTX: 4-amino-4-deoxy-10-methylpteroyl glutamic acid) is currently regarded as one of the most effective medications for the treatment of extensive and severe psoriasis. But many adverse reactions of MTX used for psoriasis have been documented. Among them, bone marrow depression reveals leukopenia leading to decreased resistance to infection, and thrombocytopenia.¹

Recently, oral etretinate (RO 10-9359) has been discovered known to affect keratinization. That is, inhibition of keratinization or antikeratinization is disclosed.² Therefore, this drug is used for the treatment of psoriasis, but side effects such as hair loss, cheilitis and xerosis are frequently encountered.³

We report herein a patient with longstanding psoriasis, who showed an acute adverse reaction which was presumed to be due to MTX and etretinate.

REPORT OF A CASE

A 49-year-old Caucasian male patient with a 25-year history of generalized psoriasis was admitted to our hospital on February 3, 1987 because of fever of 3 days' duration, general weakness and diffuse hair loss on the scalp.

Twelve days before admission, the patient, who weighed 57 kilograms, had self-administered etretinate PO. (Tegison®, 25mg/day), prednisolone PO. (50mg/day), and MTX PO. (15mg/day) for 5 days. He had no past history of illness except psoriasis.

Physical examination revealed remarkable skin eruptions in the form of erythematous eroded patches which were partially covered with crust and combined with multiple tiny pustules on the lower extremities and perianal region (Fig. 1, 2a) and slightly diffuse hair loss on the scalp. Multiple ulcerations with severe pain in the labial mucosa were also seen (Fig. 3a).
Fig. 1. Erythematous eroded patches on the perianal area.

Fig. 3. Diffuse ulcerative patches with pus on the labial mucosa (a). Improved state after 2 weeks of treatment (b).

Fig. 4. Subcorneal pustules in the epidermis and perivascular infiltration of lymphocytes in the upper dermis (H & E stain, x200).

Fig. 2. Purpuric scaly patches with tiny pustules on the right lower leg (a). Improved state after 2 weeks of treatment (b).
Table 1. Treatment and follow-up of leukocyte and platelet counts

<table>
<thead>
<tr>
<th>Hospital Day</th>
<th>1st</th>
<th>4th</th>
<th>5th</th>
<th>6th</th>
<th>10th</th>
<th>12th</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte (×10³/mm³)</td>
<td>2,000</td>
<td>1,500</td>
<td>1,300</td>
<td>1,000</td>
<td>2,500</td>
<td>4,200</td>
</tr>
<tr>
<td>Platelet (×10³/mm³)</td>
<td>137,000</td>
<td>52,000</td>
<td>29,000</td>
<td>46,000</td>
<td>188,000</td>
<td>436,000</td>
</tr>
<tr>
<td>Treatment</td>
<td>Antibiotics</td>
<td>Analgesics</td>
<td>KETOCONAZOLE</td>
<td>Transfusion of concentrated platelets</td>
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Laboratory evaluation revealed an abnormal blood cell count which showed leukopenia (2,000/mm³) and thrombocytopenia (137,000/mm³). The VDRL test was 1:2 reactive, suggesting biologic false positive reaction by the negative TPHA reaction. The following laboratory examinations were normal or negative: urinalysis, liver function test, fasting blood sugar, serum electrolytes (Na⁺, K⁺, Cl⁻), serum immunoglobulin, Trosette test, chest PA, and electrocardiography. The patient showed normal response to the delayed cutaneous hypersensitivity test (multiwell CMI). The microtiter particle agglutination test for acquired immunodeficiency syndrome was negative.

Direct KOH examination form the lesions of the oral cavity and lower extremities revealed hyphal elements with a few budding yeast cells. *Candida albicans* was isolated on Sabouraud glucose agar media at room temperature.

A biopsy specimen was obtained from the lesion of the right lower leg. Histopathological examination showed a subcorneal pustule in the epidermis and perivascular infiltration of lymphocytes in the upper dermis (Fig. 4).

Follow-up examination of the complete blood cell count (CBC) on the sixth hospital day showed decreased leukocyte and thrombocyte counts, which were 1,000/mm³ and 46,000/mm³, respectively (Table 1).

The patient was treated with a transfusion of concentrated platelets and antibiotics as well as oral ketoconazole (200mg/day) for candidiasis.

After the 10th hospital day, the number of leukocytes and thrombocytes began to increase, and subsequently his general condition and skin lesions improved. On the 12th hospital day, the CBC was within normal limits and he was discharged. He was checked at 2 week intervals at our hospital out-patient clinic after his discharge until now. His skin lesions and general condition were remarkably improved (Fig. 2b, 3b.)

**DISCUSSION**

Psoriasis is a chronic scaly erythematous disease of unknown etiology manifesting wide variation in severity, and tends to pose a difficult therapeutic problem in dermatologic clinics. As psoriasis progresses in severity and extensiveness, it also becomes less responsive to topical treatment. Therefore, systemic therapy is almost always more effective. Corticosteroids, methotrexate and psoralen plus UVA (PUVA) therapy have been used as systemic therapy for psoriasis. Recently retinoids, synthetic derivatives of vitamin A, have been used for the treatment of psoriasis. But these systemic therapies are not expected to cure the disease permanently, and frequently side effects have developed.

MTX inhibits the enzyme folic acid reductase, thus preventing DNA synthesis, so that it acts directly on the proliferating epidermal cells of psoriasis. But it can also detrimentally affect normal rapidly proliferating tissues such as bone marrow, the gastrointestinal tract and hair roots. The most commonly reported adverse reactions of MTX used for psoriasis include malaise, nausea, fatigue, redness and ulceration of mucosal tissue, chiefly the buccal mucosa, but the nasal epithelium and the conjunctiva may also be involved. After many years of MTX usage, some patients showed abnormal results of liver function studies.

Bone marrow toxicity is manifested by reticulocytopenia, which may progress to anemia, leukopenia and thrombocytopenia if the drug is continued. These effects are generally dose-related and rapidly reversible. Usually recovery is rapid, taking only several days for patients who are in good general condition, but in some cases, toxicity may be more severe and recovery is more prolonged if patients are in poor general condition, or have infection and impaired liver or bone marrow function. In general, administration of MTX must be individualized for
Each patient, carefully weighing benefits versus risks. Recently, an aromatic retinoid, oral etretinate, has been discovered to affect keratinization and has been shown to be effective in widespread psoriasis. But the exact mechanism by which etretinate exerts its therapeutic activity on psoriasis is unknown.

Probably it inhibits the activity of ornithine decarboxylase, an enzyme essential for the biosynthesis of polyamines which are known to be associated with cell growth and proliferation.

Although etretinate has been used effectively to treat psoriasis, side effects are frequently encountered. The side effects are closely related to the syndrome of hypervitaminosis A, including dryness of lips, mouth and nose, cheilitis, xerosis, desquamation of the skin, hair loss and pruritus, all of which are dose related. Systemic effects involving the liver, central nervous and skeletal systems and lipid metabolism also develop. Fortunately, except for elevations in the level of serum lipids, which are reversible, etretinate appears to cause little serious systemic toxicity.

In the recent treatment of psoriasis, etretinate has been given combined with agents, for example, topical triamcinolone acetonide, anthralin, or photochemotherapy. The simultaneous administration of MTX and etretinate provided more successful therapy. But there was no evidence for increased MTX or etretinate toxicity.

In the present case, the patient took MTX PO. 15mg/day (0.26mg/kg/day) and etretinate 25mg/day (0.4mg/kg/day) for 5 consecutive days. We presumed that he took an overdosage of MTX but a relatively low dosage of etretinate. The patient showed severe leukopenia and thrombocytopenia. We considered that these were the reflection of bone marrow depression due to the overdosage of MTX. He suffered from diffuse candidiasis involving the labial mucosa and extremities, which was probably a secondary infection due to leukopenia caused by the overdosage of MTX, although immunologic tests such as serum immunoglobulin and delayed cutaneous hypersensitivity were within normal limits. The present case also showed changes in the skin and mucous membrane, such as multiple labial ulcerations and hair loss. These changes may have been caused by MTX alone but we could not rule out that these were caused by the synergic effect of both drugs. There were abnormal findings of serum lipid and liver enzymes.

We report a patient with longstanding psoriasis, who showed presumed acute adverse reactions due to MTX and etretinate.

REFERENCES


