Co-trimoxazole (trimethoprim-sulfamethoxazole) and pyrimethamine-sulfadoxine have been recommended for treatment and prophylaxis, respectively, of Pneumocystis carinii pneumonia (PCP). However, toxic epidermal necrolysis (TEN) occurred in three of four patients with acquired immunodeficiency syndrome (AIDS) during the course of treatment or prophylaxis of PCP with these agents. On the other hand, 14 patients with PCP treated with pentamidine never developed TEN. Because the incidence of adverse skin reactions is higher among patients with AIDS than those without AIDS, and TEN is a severe, potentially fatal skin reaction, sulfonamide-containing drugs should be given cautiously to patients with AIDS.

Key words: Pneumocystis carinii pneumonia, Adverse skin reaction, Sulfamethoxazole, Sulfadoxine, Pentamidine

Co-trimoxazole (combination of 80 mg of trimethoprim and 400 mg of sulfamethoxazole per g or per tablet) is widely used for treatment and prophylaxis of Pneumocystis carinii pneumonia (PCP), an opportunistic infection which frequently occurs in immunocompromised hosts (1). Because of the low incidence of toxicity, co-trimoxazole has been recommended rather than pentamidine as the preferred drug for the treatment of PCP (2). The fixed combination of pyrimethamine (25 mg) and sulfadoxine (500 mg) (pyrimethamine-sulfadoxine) is also recommended for prophylaxis against PCP, as well as for treatment and prophylaxis of malaria (3). Although very rare, these agents are known to cause severe, sometimes fatal, skin reactions including Stevens-Johnson syndrome (erythema multiforme major) (4, 5) and Lyell's syndrome or toxic epidermal necrolysis (TEN) (4, 6, 7). The incidence of pyrimethamine-sulfadoxine related TEN among American travelers was estimated to be one per 5,000–8,000 users (4). These studies have been conducted on persons without acquired immunodeficiency syndrome (AIDS).

PCP is the most frequent opportunistic infection in patients with AIDS (8). As the number of patients with AIDS is rapidly growing every year, the frequency of co-trimoxazole and pyrimethamine-sulfadoxine being prescribed is likely also increasing. Among HIV-infected patients, one fatal case of TEN associated with pyrimethamine-sulfadoxine prophylaxis for PCP has been reported to date (9, 10). Although it is reported that the incidence of various skin reactions to co-trimoxazole among patients with AIDS is considerably higher than that among patients without AIDS, the incidence of TEN among patients with AIDS has not yet been reported.

Here, we describe TEN observed in 3 of 4 patients with AIDS who had been treated with co-trimoxazole or pyrimethamine-sulfadoxine. Based on our experience with these patients, it is recommended that these drugs are cautiously administered.
to HIV-infected patients, especially when treating those with AIDS.

CASE REPORTS

Case 1: In August 1986, a 26-year-old man was transferred to our hospital with high fever, erythema and dyspnea. A diagnosis of hemophilia A had been made at the age of 2, and blood products (coagulation factor 8) had been given once every 2–3 months. He lost 6 kg in the 6 months prior to admission. Two days before admission to another hospital, high fever and a dry cough developed, and he became dyspneic. Physical examination revealed moist rales in bilateral lungs, and several enlarged lymph nodes, about 1 cm in diameter, in both sides of the neck and inguinal regions. Chest X-ray films revealed bilateral diffuse opacity and fine reticular shadow in bilateral lung fields compatible with PCP. Oral administration of co-trimoxazole at a dose of 4 g/day was started. Two days later, the dose was increased to 10 g/day and clinical improvement was attained to some extent. Nine days after the start of co-trimoxazole treatment, erythema-like skin eruption appeared at first on the face and rapidly spread confluent over the entire skin with pain. The patient was soon transferred to our hospital. Physical examination showed a temperature of 39°C, blood pressure of 110/70 mmHg, heart rate of 96 beats/min (regular), and respirations of 22/min. He was dyspneic, and had severe stomatitis with ulcers in addition to erythema over the whole body. The arterial blood gas showed PaO₂ 52 mmHg, PaCO₂ 26 mmHg and pH 7.408. CD4+ lymphocyte count was 20 cells/µl (Table 1). Anti-HIV antibody was positive, which was confirmed by Western blot analysis. Pentamidine (4 mg/kg, i.v.) was substituted for co-trimoxazole, and prednisolone (5 mg/day) was started. In a few days, however, blisters occurred in the neck and anterior chest, which also spread rapidly over the trunk. Exfoliation of the epidermis was observed, and Nikolsky’s sign was positive. He died of respiratory failure 4 days after admission in our hospital. The drugs administered to the patient before developing TEN were co-trimoxazole (for 9 days) and antibiotics (CMX and AMK for 6 days each).

Postmortem examination revealed PCP, and esophageal and bronchial candidiasis. Pathological diagnosis of the skin lesions was TEN (Fig. 1).

Case 2: A 39-year-old man with hemophilia A was admitted to our hospital because of high fever in December 1987. The patient was well until January 1986, when he started to have recurrent diarrhea, and oral and esophageal candidiasis. He tested positive for anti-HIV antibody, which was

Table 1. Laboratory Findings on Admission

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC (x 10^4/µl)</td>
<td>469</td>
<td>194</td>
<td>365</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>13.9</td>
<td>6.5</td>
<td>13.2</td>
</tr>
<tr>
<td>WBC (µl)</td>
<td>8,400</td>
<td>1,100</td>
<td>4,200</td>
</tr>
<tr>
<td>Band (%)</td>
<td>ND</td>
<td>24</td>
<td>19</td>
</tr>
<tr>
<td>Seg (%)</td>
<td>ND</td>
<td>52</td>
<td>71</td>
</tr>
<tr>
<td>Lymph (%)</td>
<td>1.5</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>Mono (%)</td>
<td>ND</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Eosino (%)</td>
<td>ND</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Baso (%)</td>
<td>ND</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Others (%)</td>
<td>ND</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>CD4+ (/µl)</td>
<td>20</td>
<td>2</td>
<td>36</td>
</tr>
<tr>
<td>CD4+/CD8+</td>
<td>0.46</td>
<td>0.03</td>
<td>0.26</td>
</tr>
<tr>
<td>β₂ microglobulin (µg/ml)</td>
<td>ND 2.9</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>61</td>
<td>55</td>
<td>22</td>
</tr>
<tr>
<td>CRP</td>
<td>3+</td>
<td>5.09*</td>
<td>9.06*</td>
</tr>
<tr>
<td>RA</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>IgG (mg/dl)</td>
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<td>IgA (mg/dl)</td>
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<td>586</td>
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<td>IgM (mg/dl)</td>
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<td>184</td>
<td>124</td>
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<tr>
<td>IgE (IU/ml)</td>
<td>ND</td>
<td>ND</td>
<td>30</td>
</tr>
</tbody>
</table>

* , mg/dl; ND, not done

Fig. 1. Microscopic findings of a bullous skin lesion in case 1. Epidermis is completely detached from underlying tissue. Cellular infiltration was minimal.
confirmed by Western blot analysis. In October 1987, azidothymidine (600 mg) was administered, but it was discontinued 4 wk later because of neutropenia. Because the CD4⁺ lymphocyte count and the CD4/CD8 ratio had repeatedly been less than 10 cells/μl and 0.2, respectively, administration of pyrimethamine-sulfadoxine (25 mg/500 mg) once a week was started for prophylaxis of PCP in November 1987. Ten days before admission, high fever developed and continued. Physical examination on admission showed a temperature of 39.2°C and several enlarged lymph nodes, about 1 cm in diameter, in both sides of the neck and right axilla. Bacterial pneumonia was first suspected based on the findings of chest X-ray films, and clindamycin was administered, which was discontinued four days later because it was not effective. Thus, pyrimethamine-sulfadoxine was the only drug which was continued regularly. One week after admission, an induration of the skin with central necrosis was noticed on the right side of the chest wall. Several days later, erythema and blisters appeared on his anterior chest, and spread over the trunk in a few days. Pyrimethamine-sulfadoxine was discontinued after the sixth dose, but some of the blisters broke open and exfoliated. Meanwhile, he progressively became disoriented, confused and semicomatous, and died of cachexia and HIV-encephalitis in January 1988.

Postmortem examination revealed malignant lymphoma involving the skin, liver, spleen, adrenal glands, etc., severe cytomegalovirus infection in bilateral adrenal glands and aseptic meningoencephalitis. Pathological examination of the bullous skin lesions confirmed the diagnosis of TEN. Lymphoma cells in the skin were found in the induration under the ulcerated area, but not in other parts of the skin.

Case 3: In April 1988, a 30-year-old man with hemophilia B was admitted to our hospital because of fever, erythema and blisters on the face, neck and anterior chest. He tested positive for anti-HIV antibody, which was confirmed by Western blot analysis. In August 1987, he had been admitted to our hospital because of PCP, and treated with pentamidine. Ever since October 1987, when he recovered from PCP, he received azidothymidine (600 mg/day) every day and pyrimethamine-sulfadoxine (25 mg/500 mg) once a week for prophylaxis of recurrence of PCP. No other drugs had been prescribed. In April 1988, high fever, erythema and blisters rapidly appeared first on the face, and spread over the entire skin within a few days. Physical examination on admission showed a temperature of 39.4°C, heart rate of 120/min, confluent erythema with positive Nikolsky's sign, and numerous blisters on the whole body surface. CD4⁺ lymphocyte count was 36 cells/μl, and the CD4/CD8 ratio was 0.26 (Table 1). The skin lesions were typical for TEN, and the diagnosis was confirmed by an experienced dermatologist. Azidothymidine and pyrimethamine-sulfadoxine was discontinued; the latter drug was administered a total of 23 times. For the treatment of TEN, 100 mg of prednisolone was administered. The blisters, however, increased in number and size, and subsequently ruptured. The dose of steroid was in-

![Fig. 2. Skin lesions on lower extremities in case 3. A) Lateral view of the right leg. Dark spots are the crusts of dried blisters. New skin had grown on the posterior half of the thigh and calf (bright area of the leg). The dead epidermis on the anterior half of the thigh and leg (dark area) peeled off later. B) Lesions on the sole. The epidermis on the sole was also involved, and completely peeled off later.](image-url)
creased to an amount equivalent to 200 mg of prednisolone. With this high-dose corticosteroid therapy, the temperature decreased, and the blisters on the lower extremities became dry leaving crusts (Fig. 2). At this time, an entire skin layer on the upper half of his body had peeled off, sparing only the hairy scalp. The skin on the lower half of the body also scaled off later.

He completely recovered from severe TEN in May 1988, but unfortunately died of intracranial hemorrhage in June 1988. Postmortem examination confirmed cerebellar hemorrhage, and pulmonary aspergillosis with concomitant cytomegalovirus infection. The skin lesions had been healed leaving no abnormality.

**DISCUSSION**

TEN, which occurs in ten cases per million persons per yr (12), is a rare but very severe skin reaction characterized by 1) widespread blisters with morbilliform or confluent erythema, 2) sudden onset and generalization within a few days, and 3) the histologic findings of full-thickness epidermal keratinocyte necrosis, and a minimal to absent dermal infiltrate (13). The clinical courses and manifestations of the three cases presented here were typical of TEN. The symptoms were very severe in cases 1 and 3, and moderate in case 2. The diagnosis was pathologically confirmed in cases 1 and 2. Although biopsy was not carried out in case 3, the clinical findings in case 3 were the most convincing among these three cases, and the diagnosis was confirmed by an experienced dermatologist.

The syndrome recognized in babies and children is typically due to a circulating staphylococcal epidermolytic toxin, and is often referred to as staphylococcal scaled skin syndrome (14). In adults, however, adverse drug reactions are the principal cause of the syndrome; sulfonamides including co-trimoxazole and pyrimethamine-sulfadoxine are the most frequent drugs responsible (4, 6). Details of pathogenesis of the syndrome in adults is not known, but it is generally assumed to be an immunologically mediated reaction in the skin (13); a type IV or delayed type reaction has been proposed as the immunologic mechanism for the syndrome (15). In this connection, it is interesting to know that the patients with HIV infection, especially those with advanced disease have abnormalities not only in cellular immunity but also in humoral immunity (16–19); various autoimmune phenomena have been associated with HIV infection (20, 21). The manifestations include arthritis, myositis, vasculitis, the sicca syndrome, and relevant autoimmune phenomena such as the appearance of antinuclear antibodies, antibodies against platelets, lymphocytes, granulocytes and phospholipids, circulating immune complexes, rheumatoid factor, positive Coombs test, and so on (21). These abnormalities in patients with AIDS may be somehow linked to the increased skin reactivity against co-trimoxazole (11), and to the production of drug-dependent antiepidermal antibodies, which are occasionally found in patients with TEN (22). Although these immunological abnormalities were not investigated in the present cases, the levels of IgG and IgA were elevated, suggesting the presence of abnormalities in humoral immunity.

In our hospital, a total of 26 patients with AIDS have been treated. Co-trimoxazole was prescribed to one patient only (case 1) for the treatment of PCP, and pyrimethamine-sulfadoxine to three patients including cases 2 and 3 presented here. No other patients received sulfonamide-containing drugs. Thus, three of four patients with AIDS who received sulfonamide-containing drugs exclusively developed TEN as described above. After we recognized the third case, we stopped using sulfonamide-containing drugs, and pentamidine treatment was chosen instead. Subsequently 14 patients with PCP have been treated with pentamidine, and none of them developed TEN. The other drugs administered to the present three cases have not been reported to cause TEN. Therefore, together with the previous observation that sulfonamides are most frequently responsible for TEN (4, 6, 7), it may be feasible to assume that co-trimoxazole and pyrimethamine-sulfadoxine are responsible in these cases also.

Because of severe cutaneous reactions, seven American travelers died of TEN and Stevens-Johnson syndrome, thus the routine weekly use of pyrimethamine-sulfadoxine for the prophylaxis of malaria have been warned (4). As for AIDS, four surviving cases of Stevens-Johnson syndrome and one fatal case of TEN associated with pyrimethamine-sulfadoxine was reported by CDC
Toxic Epidermal Necrolysis in AIDS

(9, 23). When an adverse reaction occurs, sulfadoxine has the disadvantage of a longer half-life than sulfamethoxazole. Although no such severe reaction has been reported since then, based on our experience it is important to warn that TEN may occur rather frequently among patients with AIDS when sulfonamides are used. This is supported by a retrospective observation by Gordon et al (11) in which only five of 37 patients with AIDS who started with co-trimoxazole treatment were able to complete the treatment. In 29 patients drug toxicity occurred, and in 19 the treatment was changed due to adverse reactions that included rash, fever, and neutropenia; pentamidine was less toxic, and more tolerable (11).

TEN is very severe and can be fatal in itself. Moreover, because most of the skin is peeled off and, therefore, the mechanical barrier against microbial invasion is broken, the risk of a secondary infection is quite high, especially in such immunocompromized host as AIDS patients. Thus, although pentamidine shows several other side effects, pentamidine may be recommended as a choice for the treatment and prophylaxis of PCP in patients with AIDS.

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