CASE REPORT

Use of etanercept to treat toxic epidermal necrolysis in a human immunodeficiency virus-positive patient

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ARTICLE INFO

Article history:
Received: Aug 8, 2011
Revised: Nov 15, 2011
Accepted: Apr 13, 2012

Keywords:
etanercept
human immunodeficiency virus
Stevens–Johnson syndrome
toxic epidermal necrolysis

ABSTRACT

Toxic epidermal necrolysis (TEN) is an uncommon and severe cutaneous adverse drug reaction that causes disseminated necrosis of epidermal cells and mucocutaneous detachment. Here, we report the case of a 32-year-old man with human immunodeficiency virus infection who presented with generalized violaceous macules and blister formation 4 days after the administration of mefenamic acid and amoxicillin for a dental procedure. Additional symptoms included oral ulcers and conjunctivitis. Results of skin biopsy were compatible with Stevens–Johnson syndrome (SJS). SJS progressed to TEN within 2 days. Etanercept treatment showed a dramatic improvement in the symptoms of mucocutaneous lesions. To our knowledge, this is the first report on the treatment of TEN using etanercept in a human immunodeficiency virus-positive patient.

Introduction

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous adverse drug reactions that cause disseminated epidermal necrosis. Both conditions are associated with rapid generalized mucocutaneous detachment and can potentially result in death.1

Individuals infected with human immunodeficiency virus (HIV) are particularly susceptible to the development of severe adverse cutaneous drug reactions such as TEN and SJS.2,3 Patients with SJS or TEN often receive systemic steroids for treating skin inflammation. However, complications because of steroid use such as infections and poor wound healing are a concern. Here, we report the case of an HIV-positive patient diagnosed with TEN based on the results of skin biopsy. When the patient was treated with etanercept, complete resolution of symptoms with no complications was seen.

Case report

A 32-year-old, HIV-seropositive but asymptomatic man presented to our emergency department with generalized skin eruptions and fever that had persisted for 1 day. He had been diagnosed with HIV infection in 2004 and had started receiving highly active antiretroviral medications in 2006. He had stopped taking his medication and missed his HIV follow-up appointment 7 months before he presented to our emergency department. He had no occurrence of opportunistic infections during the previous 7 months.

The patient had undergone a dental procedure 4 days before presenting to our facility. Mefenamic acid and amoxicillin were prescribed for prophylactic use on the same day. He was not taking any Chinese herbs, health products, or other drugs. A high fever (>40°C) was noted 1 day before presentation. The sudden onset of generalized, painful, erythematous skin eruptions with blisters developed over the following 6 hours.

Physical examination revealed dissemination of generalized erythematous macules with a central purpuric hue (termed “atypical target lesions”) on the patient’s trunk, on all four limbs, and face (Figure 1). Some macules were confluent, forming patches with bullae. Epidermal detachment involved 9% of the total body surface area (TBSA). There were multiple ulcers on the lips and oral mucosa. Bilateral conjunctivitis was also noted. Lymphadenopathy was not observed. Results of laboratory examinations showed a normal white blood cell count (7800 cells/µL; normal range, 3900–10,600 cells/µL), elevated serum creatinine level (1.36 mg/dL; normal range, 0.64–1.27 mg/dL), elevated alanine transaminase level (42 U/L; normal range, 0–36 U/L), normal blood urea nitrogen (13.6 mg/dL; normal range, 6–21 mg/dL), elevated C-reactive protein level (10.26 mg/L; normal range, <5 mg/L), normal fasting blood glucose level (90 mg/dL; normal range, 70–120 mg/L).
dL), decreased CD4+ T cells (6.6%; normal range, 23–53%), and an elevated concentration of HIV RNA (20,789 copies/mL; normal range, negative). Results of arterial blood gas examination showed a normal bicarbonate level (25.9 mm/L; normal range, 22–26 mm/L), while urine analysis revealed the presence of 1+ protein and trace glucose but not pyuria. A chest X-ray was normal, and the Tzanck smear test showed a negative morphological pattern for herpes virus. Results of skin biopsy showed a detached and totally necrotic epidermis and mild perivascular mononuclear cell infiltrates in the dermis (Figure 2).

The pathological findings were compatible with SJS. Blood culture was negative for microbial growth. A diagnosis of SJS with a SCORTEN score of 1 was thus established. Results of lymphocyte transformation test were positive for amoxicillin and negative for mefenamic acid (Table 1). The patch test was also positive for amoxicillin and negative for mefenamic acid. Therefore, the probable causative agent was amoxicillin.

The patient received one dose of intravenous methylprednisolone (20 mg) on the 2nd day of hospitalization (Figure 3). The absolute CD4+ T-cell count at that time was 66 cells/µL (normal range, >200 cells/µL). To avoid a potential HIV outbreak, we discontinued the use of systemic steroid. The epidermal detachment progressed to 40% TBSA on the 3rd day of hospitalization. The patient’s diagnosis was changed to TEN. The fever, general malaise and appearance of new atypical target lesions continued to progress. Injections of 50 and 25 mg of etanercept were administered on the 3rd and 5th day of hospitalization, respectively. The antiretroviral agents nevirapine and abacavir/lamivudine were prescribed for HIV control on the 4th day of hospitalization. The tumor necrosis factor-α (TNF-α) level was 26.6 pg/mL (normal range, <8.1 pg/mL) on the same day. The absolute CD4+ T-cell count was 85 cells/µL on the 6th day of hospitalization. No fever and no new cutaneous lesions were observed after the 6th day of hospitalization. Re-epithelialization of the erosions occurred on the 8th day of hospitalization (Figure 4). Total resolution of the mucocutaneous lesions was noted 14 days after treating the patient with etanercept. Furthermore, the patient’s absolute CD4+ T-cell count had increased to 202 cells/µL by the 14th day of hospitalization. He was discharged in a stable condition.

Discussion

SJS and TEN constitute life-threatening, severe cutaneous adverse drug reactions and reflect a spectrum of the same condition. By definition, SJS causes epidermal detachment in <10% of the TBSA, whereas TEN involves >30% of the TBSA; overlapping SJS/TEN affects 10%–30% of the TBSA cases. Clinically, SJS and TEN are characterized by the sudden onset of fever, followed by the development of generalized erythematous to violaceous maculopapules with blister formation. In addition, conjunctivitis and oral or genital ulcers may also develop.

HIV-seropositive patients are more susceptible to cutaneous adverse drug reactions than the general population are. Furthermore, HIV-positive individuals have been shown to have a poorer prognosis and longer hospitalization period than those who are HIV negative. The exact mechanisms underlying this augmented reaction in HIV-positive patients are still unclear, but...
Table 1: Increases in the stimulation index determined by lymphocyte transformation tests.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Cytokine</th>
<th>GNLY (^a)</th>
<th>MIP-1(\alpha) (^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>1.45</td>
<td>1.64</td>
<td></td>
</tr>
<tr>
<td>Mefenamic acid</td>
<td>0.81</td>
<td>0.93</td>
<td></td>
</tr>
</tbody>
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\(^a\) Data are reported as “fold” increases in the stimulation index determined by lymphocyte transformation tests.

exposure to multiple drugs and the presence of immune disturbances may be contributing factors.\(^5\) CD4\(^+\) T-cell counts may be altered by SJS/TEN. Roujeau et al\(^8\) showed that CD4\(^+\) T-cell counts decreased in patients with TEN. Azukizawa demonstrated that in vivo deletion of CD4\(^+\) T cells induced TEN in transgenic mice.\(^9\) However, Nishio et al\(^10\) showed no statistically significant changes in CD4\(^+\) T-cell numbers in patients with SJS. Jao et al\(^11\) reported decreased CD4\(^+\) cell counts during the onset of SJS in an HIV-infected patient and elevation of CD4\(^+\) cell counts after full recovery from SJS.

The treatment strategy for SJS/TEN involves eliminating the causative agents and decreasing the inflammatory damage to the epidermis. Systemic steroid administration is frequently used for SJS/TEN. However, use of systemic steroid in HIV-positive individuals is still controversial.\(^12\) Even a transient increase in HIV RNA levels was found after the administration of a systemic steroid.\(^14\) Moreover, it has been reported that continued systemic steroid administration is not associated with improvements in mortality rates or wound healing in patients with SJS/TEN.\(^17\)

Infiltrates of cytotoxic T lymphocytes and increased amounts of TNF-\(\alpha\) were observed in the epidermis of TEN lesions.\(^15\) Paul et al\(^15\) elucidated that TNF-\(\alpha\) released by cytotoxic T lymphocytes could induce epidermal apoptosis by binding to TNF-\(\alpha\) receptors on the cell surface of keratinocytes in TEN lesions. Then, extensive epidermal destruction began. Thus, TNF-\(\alpha\) inhibitor may be an effective agent to decrease epidermal apoptosis among patients with TEN. Furthermore, higher serum levels of TNF-\(\alpha\) are associated with HIV progression, including reduced immunocompetency and debilitating symptoms such as fever and cachexia.\(^16\) Etanercept is a recombinant fusion protein that acts as a TNF-\(\alpha\) inhibitor. The structure of etanercept includes a soluble TNF-\(\alpha\) receptor linked to the Fc subunit of human immunoglobulin G1.\(^17\) Etanercept has been used for the treatment of TEN.\(^18,19\) Infection and malignancy are the main concerns over the use of etanercept. However, Ting et al\(^20\) reviewed studies before 2005 and reported that administration of TNF-\(\alpha\) antagonists to HIV-positive patients did not result in increases in morbidity and mortality rates, even when accompanied by a decrease in CD4\(^+\) cell counts or increased HIV RNA levels. Cepeda et al\(^21\) also reported stable CD4\(^+\) T cell counts and HIV viral load level without any other significant adverse effects in eight HIV-positive patients with rheumatic disease who underwent anti-TNF therapy and were monitored for 28.1 months. Out of these eight patients, only four received etanercept, whereas the other four received etanercept and other TNF-\(\alpha\) inhibitors.\(^21\) Results of many other studies neither showed increased HIV viral load nor other detectable side effects in HIV-positive patients with concurrent rheumatoid arthritis, psoriasis, or hepatitis C infection under the treatment of etanercept.\(^16,22,23\) Wallis et al\(^24\) even showed a 25% increase in CD4\(^+\) T-cell count and stable HIV viral load in 16 HIV-infected patients undergoing etanercept treatment. TNF-\(\alpha\) could be a target for the treatment of patients with concurrent HIV and SJS/TEN. Our patient did not undergo an HIV follow-up for 6 months before presenting to our emergency department. Thus, we were unable to identify whether the etanercept injections impacted CD4\(^+\) cell counts or HIV RNA levels. However, the patient’s CD4\(^+\) T-cell counts increased, and complete healing of the mucocutaneous lesions occurred within 2 weeks of etanercept treatment.
To the best of our knowledge, no previous reports describe the use of etanercept to treat SJS/TEN in patients with HIV/AIDS. We show here that short-term etanercept treatment for SJS/TEN in patients with HIV/AIDS can be highly successful. Large randomized controlled studies should be performed to confirm the safety and efficacy of etanercept to treat SJS/TEN in patients with HIV/AIDS.

References