CASE REPORT

Toxic epidermal necrolysis secondary to *Mycoplasma pneumoniae* and herpes simplex virus infection

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Summary  Toxic epidermal necrosis (TEN) is a life-threatening skin reaction associated with a high mortality rate. Most TEN is induced by drugs, but some cases are caused by other insults. *Mycoplasma pneumoniae* and herpes simplex virus are the most common infectious pathogens associated with TEN. In identifying the etiology of TEN, it is crucial to include not only a detailed drug history but also potential infection sources. Any suspicious infections should be treated in a timely and efficient manner to improve survival rates. In this article, we report on five patients who developed TEN related to *M. pneumoniae* and herpes simplex virus infections. We also reviewed the relevant literature. We performed a retrospective medical chart review of five patients with TEN, which was considered secondary to *M. pneumoniae* and herpes simplex virus infections. We compared patients with infection-induced and drug-induced TEN. We found that patients with infection-induced TEN were younger in age and had lower SCORTEN scores, less renal dysfunction, shorter hospitalization periods, and higher survival rates compared with patients with drug-induced TEN. Identifying the etiology of TEN requires the inclusion of not only a detailed drug history but also infection sources, such as *M. pneumoniae* and herpes simplex virus. Our findings corroborate previously reported clinical
1. Introduction

Toxic epidermal necrolysis (TEN) and Stevens–Johnson syndrome (SJS) are uncommon but life-threatening skin conditions. Skin detachment of < 10% of total body surface area (TBSA) is classified as SJS, > 30% detachment is classified as TEN, and between 10% and 30% detachment is classified as overlap SJS/TEN.\(^1,2\) Most TEN has an acute onset and is a result of an adverse drug reaction. However, other conditions, such as infections, can also be a trigger. Of the 101 patients with TEN in our previous study, five patients had TEN caused by infection.\(^3\) Of these five patients, three had TEN associated with *Mycoplasma pneumoniae* and two had TEN associated with herpes simplex virus infection.

*M. pneumoniae* is a well-known cause of SJS, which is an intracellular pathogen responsible for atypical respiratory infection. It has been reported as the most common infectious agent associated with SJS affecting children and young adults.\(^4\) It is rarely the cause of TEN.\(^5,7\) Herpes simplex virus is located in the basal keratinocyte and lower spinous cell layers. Expression of viral DNA fragments in the keratinocyte layer leads to activation of CD4 positive T-helper cells, which induce various reactions, including cytokine production and subsequent inflammatory response. CD4 positive T-helper cells are also the predominant cells in the blister fluid of patients with TEN,\(^8\) and the cytokine they produce is responsible for the pathologic findings in skin lesions.\(^9\) It is crucial that an etiology of TEN includes not only a detailed drug history but also infection sources. In this article, we report on five patients in whom TEN developed because of *M. pneumoniae* and herpes simplex virus infections, and we review the relevant literature. Additionally, we compare patients with TEN associated with viral infections and patients with drug-induced TEN.

2. Patients and methods

A retrospective medical chart review was performed for five patients admitted between January 1992 and December 2009 to a burn intensive care unit (BICU) with TEN, which was considered secondary to *M. pneumoniae* and herpes simplex virus infections.

The severity of TEN was measured using the patients’ SCORTEN scores. The SCORTEN (Severity-of-Illness Score for Toxic Epidermal Necrolysis) score is an illness severity index used exclusively for TEN developed by Roujeau in 2000 and is defined by the EuroSCAR group.\(^11\) The score is designed to predict the mortality rate through seven independent factors that are scored within 24 hours from patient admission (Table 1). Each factor contributes one point to the overall SCORTEN level, with a higher score correlating with a higher mortality rate. The treatment protocol that was applied for these patients with infection-induced TEN was the same as the protocol for patients with drug-induced TEN. Early diagnosis, prompt withdrawal of suspected drugs, and confirmation of possible infection sources were considered the most critical to manage this condition. Fluid resuscitation was begun after admission according to body surface defect percentage and adjusted according to urine output. Hydrotherapy was administered to all patients to remove the lytic skin carefully. Membrane dressings were used for wound care. Aquacel\(^\text{®}\) Ag Hydrofiber\(^\text{®}\) dressing (Convatec Inc. USA) or Acticoat\(^\text{®}\) (Smith & Nephew, Inc.) USA was used routinely for both patients with drug- and infection-induced TEN. These were most effective for children because of their poor cooperation and compliance when changing dressing. Elastic cotton bandages were then wrapped around the dressing. The dressing is changed every 2–3 days. The wound was evaluated twice per week; all dressings were removed and hydrotherapy was performed. Efficacy was determined by measuring wound healing time to achieve 95% re-epithelialization of the involved area. The database from our previously published study\(^1\) was used for comparisons between patients with infection- and drug-induced TEN, such as severity, length of hospitalization periods, and prognosis. All demographic data, including sex, age, TBSA, and SCORTEN score, and laboratory data and outcome were obtained. In this study, renal dysfunction was defined as serum creatinine 1.5 times that of known baseline or urine production of < 0.5 mL/kg for 6 hours according to the International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group.\(^10\)

2.1. Statistical analysis

Values were expressed as mean ± standard deviation. Categorical and continuous variables were compared with means and normal distributions using the Chi-square and Mann–Whitney *U* tests. Any *p* value < 0.05 were considered statistically significant.

3. Results

Three cases were diagnosed as TEN associated with *M. pneumoniae* and two were diagnosed as TEN associated with herpes simplex virus infection (Table 2). The presence of these viruses was confirmed by positive serologic findings. The patients consisted of three boys and two girls, with an average age of 8.6 years (range 6–12 years). All cases were referred to the BICU at the acute stage with an average duration from disease onset of 4.2 ± 3.1 days. The average rate of TBSA epidermal detachment among our
patients was $55 \pm 30.7\%$. The average SCORTEN score recorded on admission was $1.1^0$. All patients survived. The average hospital stay of survived patients was 16.2 days (range 10–24 days). According to our database, there were 62 patients with drug-induced TEN. A younger age (infection-induced TEN:drug-induced TEN = 8.6:61.8, $p < 0.05$); lower SCORTEN score (infection-induced TEN:drug-induced TEN = 1:3.0, $p < 0.05$); less renal dysfunction (infection-induced TEN:drug-induced TEN = 0:32.3, $p < 0.05$); shorter hospitalization period (infection-induced TEN:drug-induced TEN = 16.2:22.1, $p < 0.05$); and higher survival rate (infection-induced TEN:drug-induced TEN = 100%:48.4%, $p < 0.05$) were noted in patients with infection-induced TEN (Table 3). Infection-induced TEN manifests a less severe clinical course than its drug-induced counterpart.

### 3.1. Case 1

The patient, a 6-year-old girl, presented with a 4-day history of productive cough, headache, fever, and malaise. She was admitted to our pediatric ward on the 5th day because of a high fever of 41.6°C. The patient and family denied any drug history. One day later, severe generalized erythematous skin rashes with multiple bullae developed, covering 95% of the patient’s TBSA. Dermatologic consultation was performed and a diagnosis of TEN was considered. The patient’s SCORTEN score was 1. The patient was transferred to our BICU because of the progression of her clinical condition. In the BICU, a physical examination revealed her blood pressure was 150/100 mmHg, her pulse rate was 116 beats/min, her respiratory rate was 24 times/min, and she had developed a high spiking fever of 41°C body temperature. The patient’s chest auscultation was normal. We observed bilateral nonpurulent conjunctivitis, consulted an ophthalmologist, and administered topical antibiotics. Additionally, erosions and bullae covering the entire buccal mucosa, tongue, and lip were noted. Generalized tender erythematous macules, which progressed to blisters and denudation accompanied by the Nikolsky sign were also observed (Fig. 1). A chest X-ray revealed prominent peribronchial cuffing and bilateral lower lung field infiltration (Fig. 2). Blood, sputum, and urine cultures were all negative. However, a *M. pneumoniae*-immunoglobulin IgM test was strongly positive, but on transfer to the burn ICU, an IgG serologic test was negative, demonstrating recent infection. A skin biopsy showed total detachment, necrosis, and dyskeratosis of the epidermis with mild perivascular mononuclear cell infiltrates in the dermis (Fig. 3).

We then made a diagnosis of TEN. In the following days, antimicrobial therapy with erythromycin (250 mg twice per day) was prescribed. The wound was covered by Acticoat® (Smith & Nephew, Inc.) (Fig. 4). The condition improved each day after treatment. Eight days later, the wound became dry and a new skin island appeared. After 2 weeks, the entire wound had healed (Fig. 5). *M. pneumoniae*-IgM was then converted to positive and *M. pneumoniae*-IgM was within normal limit in serologic test. The patient survived and was discharged without complication 20 days after admission.

### 3.2. Case 2

A 7-year-old boy complained of lip swelling with crust formation for 5 days and a generalized erythematous skin rash with bullae for 4 days. His mother noted several vesicles over his upper lip and commissure after several oral aphthae had developed and his condition had deteriorated; the patient was referred to our hospital. On admission, he exhibited skin eruptions with bullae and erythema on his face and extremities, bilateral conjunctivitis, and oral ulcers. Thirty percent of his TBSA was affected. Nikolsky sign

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Cause</th>
<th>TBSA of eruption (%)</th>
<th>SCORTEN score</th>
<th>Days it took to heal up to 95%</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12</td>
<td>F</td>
<td>Mycoplasma pneumonia infection</td>
<td>90</td>
<td>1</td>
<td>14</td>
<td>Survive</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>F</td>
<td>Mycoplasma pneumonia infection</td>
<td>95</td>
<td>1</td>
<td>24</td>
<td>Survive</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>M</td>
<td>Mycoplasma pneumonia infection</td>
<td>30</td>
<td>1</td>
<td>15</td>
<td>Survive</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>M</td>
<td>Herpes simplex virus infection</td>
<td>30</td>
<td>1</td>
<td>10</td>
<td>Survive</td>
</tr>
<tr>
<td>5</td>
<td>9</td>
<td>M</td>
<td>Herpes simplex virus infection</td>
<td>30</td>
<td>1</td>
<td>18</td>
<td>Survive</td>
</tr>
</tbody>
</table>

TBSA = total body surface area.
was noted. His temperature was 38.8°C. His mother denied any previous drug history. Laboratory investigation revealed a normal result for complete blood count, differential, urinalysis, liver and renal function tests, electrolytes, and coagulation studies. However, his C-reactive protein (CRP) level was elevated to 11.9 mg/dL. His antibodies against varicella zoster virus and mycoplasma pneumonia did not increase; however, a test for herpes simplex virus-IgM was strongly positive. A dermatologist made a diagnosis of TEN and an associated viral infection. Therefore, the patient was transferred to our BICU on the 5th day of his hospital admission. His SCORTEN score was 1. The wound was covered with Aquacel Ag Hydrofiber dressing (Convatec Inc. USA). Additionally, topical treatment with acyclovir was prescribed. His condition gradually improved. On Day 13, the wound became dry and a new skin island appeared. His herpes simplex virus-IgM returned to the normal range, and his herpes simplex virus-IgG was positive. He was then transferred to a general ward and discharged 2 days later.

4. Discussion

TEN is a rare but life-threatening disorder, with an incidence estimated at 0.4–1.3 cases per million person-years.2,12 TEN is an acute condition that often results from an adverse drug reaction. The drugs linked to the majority of patients with TEN include anticonvulsants, nonsteroidal anti-inflammatory drugs, allopurinol, and some antibiotics.3 However, other conditions, such as infections, can also act as a trigger. In previous studies, several viral infections have been reported to be associated with TEN, such as the Epstein–Barr virus, cytomegalovirus, human herpes virus-6, herpes simplex virus, and human immunodeficiency virus.12,13

According to the literature, most skin reactions caused by M. pneumoniae and herpes simplex virus infections are associated with less frequent and less severe complications than those with other causes. The outcome and prognosis are typically favorable with no permanent complications.4,14 In this study, three cases were due to M. pneumoniae, and two were due to a herpes simplex virus infection, as confirmed by a positive serologic finding. We found that the five patients with infection-induced TEN were younger in age and had lower SCORTEN scores, less renal dysfunction, shorter hospitalization periods, and higher survival rates compared with patients with drug-induced TEN.

According to our results, TEN in adults is typically caused by a drug, whereas TEN in children is typically caused by an infection. The mean age of those with infection-related TEN was 8.6 ± 1.9 years, whereas the mean age of those with drug-induced TEN was 61.8 ± 19.8 years. Older age was one risk factor for a poor prognosis. Roujeau et al reported patients older than 40 years had a greater risk of death because of higher rates of underlying disease and immunodeficiency.11

The average SCORTEN score for patients with infection-induced TEN was 1. The predicted mortality rate by SCORTEN score was 3.2%.11 The actual mortality rate in our series was 0%. No permanent complications were noted.
In the current study, the SCORTEN scores among patients with infection-induced TEN was 1, whereas the SCORTEN score among patients with drug-induced TEN was 3, which implies that the patients with infection-induced TEN had superior outcomes compared with those with drug-induced TEN.

No renal dysfunction was found in the patients with infection-induced TEN; however, a 32.3% rate of renal dysfunction was noted in the patients with drug-induced TEN. The higher rate of renal dysfunction among the patients with drug-induced TEN may be attributable to a higher rate of renal failure compared with those with infection-induced TEN. The aforementioned higher rates of renal failure are likely a result of the tendency in Chinese society to use Chinese medication or herbs or multiple drugs instead of seeking medical assistance. This tendency can compound problems, substantially impair renal function, and deteriorate a patient’s general condition. In our previous study, we observed that kidney dysfunction is one of the most crucial factors affecting outcome in patients with TEN. A higher renal dysfunction rate is a likely explanation for lower survival rates among patients with drug-induced TEN compared with those with infection-induced TEN.

The treatment of TEN poses a great challenge because of the rapid onset and progression of skin exfoliation with sepsis. Unfortunately, even with the advances in modern medicine, including improvements in intensive care, development of new dressing material and systemic therapies such as glucocorticoid and intravenous Ig, the mortality rate for TEN is still high and definitive treatments for TEN remain controversial. No optimal treatment protocol exists for TEN. In our BICU, no differences exist between the protocols for initial resuscitation for patients with drug- and infection-induced TEN. Continuous monitoring ensures adequate treatment of fluid and electrolyte imbalance as well as local and systemic infection. Interdisciplinary cooperation between dermatologists, ophthalmologists, intensive care physicians, and burn surgeons is also critical. Early confirmation of the causative agent of TEN is a crucial step for superior prognosis of infection-induced TEN because it enables the early prescription of antiviral drugs to stop severe cutaneous reactions. According to a recent study, pathogens are increasingly being identified as

![Figure 1](image1.png)  
**Figure 1**  Patient with toxic epidermal necrolysis related to *Mycoplasma pneumoniae* infection. Generalized erythematous macules and blisters over about 95% of total body surface area, including the lip and oral mucosa.

![Figure 2](image2.png)  
**Figure 2**  Chest X-ray plain film on the 1st day after admission revealed peribronchial thickening.
causative agents for severe mucocutaneous blistering reactions mimicking life-threatening severe cutaneous adverse reactions. Any diagnosis or treatment delay causes a severe cutaneous adverse reaction to eventually progress to SJS or TEN.

One major drawback of this study is that the sample size of patients with infection-induced TEN ($n = 5$) was too small for the results to be considered statistically significant. Despite the small sample size, comparative analysis was performed between patients with drug-induced TEN and those with infection-induced TEN. In this regard, the results are obvious and the first of their kind in Taiwan.

In conclusion, identifying the etiology of TEN requires the inclusion not only of a detailed drug history, but also the infection sources, including $M. pneumoniae$ and herpes simplex virus. Our findings corroborate previous reports on the clinical and etiologic associations of TEN. $M. pneumoniae$ and herpes simplex induced TEN manifested less severely than its drug-induced counterpart.

Figure 3  (A) Histopathology of toxic epidermal necrolysis showed that the epidermis is separated from the underlying dermis (black arrow; hematoxylin & eosin, 40×). (B) At higher magnification, the denuded dermis revealed dyskeratosis of the epidermis with mild perivascular mononuclear cell infiltrates in the dermis (hematoxylin & eosin, 400×).

Figure 4  The wound was treated with Acticoat.

Figure 5  All wounds had almost healed by Day 8, except for those on bilateral lower limbs.
References


