CLINICAL RESEMBLANCE OF WIDESPREAD BULLOUS FIXED DRUG ERUPTION TO STEVENS-JOHNSON SYNDROME OR TOXIC EPIDERMAL NECROLYSIS: REPORT OF TWO CASES

Tzu-Kai Lin, Mark Ming-Long Hsu, and Julia Yu-Yun Lee

Abstract: Widespread bullous fixed drug eruption (FDE) is the most severe form of FDE and may be mistaken clinically for Stevens-Johnson syndrome or toxic epidermal necrolysis (SJS/TEN). We report two cases of generalized bullous drug eruption with extensive epidermal necrosis and detachment mimicking SJS/TEN overlap and TEN, respectively. The first patient, a 78-year-old man, developed SJS/TEN-like eruption with widespread dusky red patches and denuded areas shortly after taking multiple nonsteroidal antiinflammatory drugs (NSAIDs). Histopathology showed vacuolar interface dermatitis with numerous necrotic keratinocytes and a superficial and deep perivascular infiltrate containing lymphocytes, eosinophils, neutrophils and melanophages. These findings are consistent with FDE. The second patient, a 61-year-old woman, had three episodes of near-total body epidermal detachment shortly after taking NSAIDs. TEN was diagnosed clinically in all three episodes without pathologic confirmation. FDE was suspected due to lack of involvement of two mucosal sites and uneventful recovery. These cases highlight the importance of considering severe bullous FDE in the differential diagnosis of SJS and TEN, and the necessity of skin biopsy in such cases.

Fixed drug eruption (FDE) is a peculiar drug reaction that tends to recur in identical sites each time the responsible drug is taken. It is characterized by solitary or multiple, round or oval, erythematous patches with dusky red centers, some of which may progress to bulla formation. FDE lesions usually resolve in 7 to 10 days, often leaving behind hyperpigmentation. With repeated challenges, additional patches or blistering lesions may arise and may evolve into a severe generalized bullous form of FDE [1]. In a series of 86 cases of FDE reported in 1985, 16 were of generalized bullous type [2]. Because this severe form of bullous FDE may mimic toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) clinically, misdiagnosis is possible.

Two additional cases of TEN-like bullous FDE were reported in 1988 [1]. TEN was initially diagnosed, but the skin biopsy indicated FDE. Complete re-epithelialization occurred within 10 days in both patients. The authors suggested that TEN-like FDE might be associated with a more favorable prognosis than TEN, although they stressed the need for further studies of such cases in order to verify potentially important differences in prognosis. Our review of the literature found no subsequent reports focusing on this issue. It is possible that TEN- or SJS-like bullous FDE is rare or has been underdiagnosed. We report two cases of severe bullous drug eruption with extensive epidermal necrosis and detachment mimicking SJS/TEN overlap and TEN, respectively. The diagnosis of FDE was supported by pathologic findings in the first case, but the diagnosis in the second case remained speculative due to the lack of a skin biopsy. These case reports may help bring attention to the importance of recognizing this severe variant of FDE and the need for skin biopsy in patients with SJS- or TEN-like eruption.
Case Reports

Case 1
A 78-year-old man was admitted in April 2000 due to a widespread skin eruption after taking nonsteroidal anti-inflammatory drugs (NSAIDs). The patient had been taking rifampin, ethambutol and pyridoxine for pulmonary tuberculosis for 1.5 months prior to the admission. There was no known drug allergy. Twenty days prior to admission, the patient experienced itching at all extremities within a few hours after taking diclofenac, naproxen and furosemide for lower back pain, followed by the appearance of a widespread erythematous rash on the face and trunk 2 days later. He stopped taking the medication 3 days later. Physical examination on admission revealed erosions on the lips and widespread coalescing erythematous and dusky red patches on the trunk and the extremities. Epidermal detachment and denuded areas were noted on the neck, upper chest and forearms (Fig. 1A), affecting about 20% of the body surface area (BSA). There were violaceous patches over the hands and feet (Fig. 1B). Nikolsky’s sign was negative. Under the impression of overlap SJS/TEN, methylprednisolone 20 mg bid was initiated on day 1 and the lesions were completely re-epithelialized by day 10. Skin biopsy specimens from the abdomen and right forearm revealed vacuolar interface dermatitis with extensive necrosis of keratinocytes in the epidermis, and a superficial and deep perivascular and interstitial mixed inflammatory cell infiltrate composed of lymphocytes, histiocytes, numerous eosinophils, neutrophils and melanophages (Fig. 2). Patch test and open application test were performed on day 17 using separate preparations of 25% naproxen, 25% diclofenac and 25% furosemide in petrolatum, on normal skin and lesion skin, respectively. The drugs were applied bid for 3 days in the open test, and both tests showed negative results at 72 hours.

Case 2
A 61-year-old woman was admitted on three separate occasions, each time with a widespread skin eruption after taking NSAIDs. The patient had been taking oral analgesics irregularly for rheumatoid arthritis over the past 6 years. There was no known drug allergy. In her first episode of drug reaction in 1991, extensive coin-sized erythema with tingling sensation developed within hours after taking sodium salicylate and ketoprofen for abdominal pain and fever. The rash became generalized with extensive detachment and loss of the epidermis involving more than 50% of the BSA. The face and upper chest were spared. She was admitted to the burn center and received methylprednisolone 20 mg bid for 8 days, then 20 mg qd for 1 further week. Re-epithelialization started on day 8 and was complete in 2 weeks. The second episode occurred 3 years later, in 1994, shortly after taking furosemide, garamycin and ketoprofen. She was admitted 2 days after the onset of symptoms with numerous large bullae and erosions. The denuded area and epidermal detachment

![Fig. 1. Case 1. A) Diffused dusky erythema with or without crusts on the anterior trunk, and B) erythema and violaceous patches on the hands.](image-url)
involved 10% and 35% of BSA, respectively. Methylprednisolone 20 mg qd was given for 3 days. Re-epithelialization began on day 9 and was complete by day 18. The third episode occurred hours after taking a single dose of flufenamic acid and acetaminophen in 1996. Bullae and epidermal detachment first appeared on the knees, then spread rapidly to involve 95% of the BSA in 3 days. When she was standing, the entire detached epidermal sheet slipped down her body like loosely fitting clothes (Fig. 3). Methylprednisolone was administered for 2 days: 48 mg on day 1 and 24 mg on day 2. Re-epithelialization started from day 6 and was complete by day 17. In all three episodes, the conjunctiva and oral mucosa were spared, but the anogenital mucosa was affected. The eruption resolved without postinflammatory hyperpigmentation. TEN was diagnosed in all three episodes without histopathologic confirmation.

Discussion

TEN is the most severe form of drug eruption [3, 4]. It represents the extreme expression in the spectrum of erythema multiforme (EM), SJS and TEN. TEN is defined as extensive confluence of macules or flat atypical targetoid lesions, resulting in epidermal detachment over 30% of the BSA [5]. SJS is defined as epidermal detachment over less than 10% of the BSA plus widespread erythematous or purpuric macules, or flat atypical targets. When the area of detachment is between 10 and 30%, the rash is classified as SJS/TEN overlap. FDE appears to have a similar spectrum of severity, ranging from isolated patches to generalized bulous lesions, with the most severe form indistinguishable from TEN clinically. Although the bullous form of FDE is well recognized, only a few studies have emphasized its clinical resemblance to EM, SJS and TEN [1, 2]. Of the 86 cases of FDE reported by Kauppinen and Stubb, 16 were generalized bullous FDE [2]. The authors did not give information regarding positive history of previous FDE, mucosal involvement, duration of the bullous FDE, or pathologic findings of skin biopsies. The other two reported cases of TEN-like bullous FDE had previous episodes of FDE and the diagnoses were confirmed pathologically [1]. Clinically, these two patients developed widespread dusky red patches and flaccid blisters without mucosal involvement after taking phenytoin and trimethoprim-sulfamethoxazole, respectively. Both patients had mild constitutional symptoms and uncomplicated short clinical courses (10 days). Most importantly, their skin biopsies revealed vacuolar interface dermatitis with epidermal necrosis and a superficial and deep perivascular infiltrate of lymphocytes, eosinophils and neutrophils, indicative of FDE.

In Case 1 of this report, the initial clinical diagnosis was SJS/TEN overlap, but the histopathologic findings — specifically, a superficial and deep perivascular mixed inflammatory cell infiltrate containing eosinophils, neutrophils and melanophages — were consistent with
FDE. Furthermore, the lack of involvement of two mucosal sites was also in keeping with widespread bullous FDE. The patient made an uneventful recovery, although the clinical course was longer than 10 days. The longer duration of the disease in this patient might be related to the fact that the drugs were continued for 2 days after the onset of skin rash. Although the patient did not report a history of prior FDE, it was possible that a previous eruption had been overlooked or forgotten. Alternatively, the current eruption might in fact have been the first episode of FDE, which happened to be unusually widespread.

In Case 2, the original diagnosis was TEN in all three episodes based on the clinical findings of extensive epidermal detachment. Retrospectively, we suspect that this patient might have had TEN-like FDE, because she never had involvement of more than one mucosal site; there were no prodromal constitutional symptoms often associated with TEN; and she had rapid and uneventful recovery in all three episodes despite almost total body epidermal detachment. In TEN, at least two of the three mucosal sites (ocular, oral and anogenital) are usually involved and the mortality rate is high, estimated at 25 to 50% in the first episode [1]. Although there have been reports of patients who survived recurrent episodes of TEN [6–8], such cases are rare and it is suspected that some of these cases might be severe FDE rather than TEN [1].

Numerous drugs have been reported to cause FDE. In the study of 86 cases of FDE confirmed by oral challenge tests [2], anticonvulsants were the most common causative drugs. Of all the drugs taken prior to the onset of drug eruptions in our patients, naproxen, diclofenac [9], ibuprofen [10], acetaminophen and aspirin are known to cause FDE. On the other hand, furosemide, ketoprofen, flufenamic acid and garamycin have not been associated with FDE. Only naproxen and aspirin have been reported to induce TEN. However, a search of our department’s records from 1988 to 1999 revealed a total of 75 cases of SJS and TEN (not counting both patients in the present report); ketoprofen had been associated with one case of SJS and two cases of TEN.

In Case 2, ketoprofen was involved in the first two episodes and flufenamic acid in the third episode. Ketoprofen has a diphenylketone moiety that has been reported to be an important antigenic determinant in drug allergy [11]. Flufenamic acid has a diphenylamine moiety. Although there has been no report of cross-reaction between ketoprofen and flufenamic acid, these two NSAIDs share a diphenyl group. Thus, a cross-reaction between these two drugs seems possible but needs to be confirmed.

To determine the drug responsible for FDE, challenge with the suspected drugs is the most specific test, but is not always practical or possible. Patch test was shown to give high positive rates, 75% and 86%, respectively, in two series of patients with FDE [12, 13]. In Case 1, patch test and open application test gave negative results. These results might have been falsely negative, because a drug reaction may occur with combination preparations, not only individual constituents [14].

The cases reported here and in previous reports illustrate the importance of differential diagnosis

Table. Clinical and histopathologic differentiation of toxic epidermal necrolysis (TEN) and TEN-like fixed drug eruption (FDE)

<table>
<thead>
<tr>
<th></th>
<th>TEN</th>
<th>TEN-like FDE</th>
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<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of recurrence of</td>
<td>Usually negative</td>
<td>Often positive</td>
</tr>
<tr>
<td>generalized lesions in identical areas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin lesions</td>
<td>Generalized purpuric macules or flat atypical targets with epidermal detachment, spreading from the face and chest to the trunk and extremities</td>
<td>Widespread large, ill-defined, dusky-red patches and flaccid blisters commonly involving the acral parts, genitals, and intertriginous sites</td>
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<tr>
<td>Involving 2–3 mucosal sites</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>Prominent</td>
<td>Mild</td>
</tr>
<tr>
<td>Recovery</td>
<td>2–6 weeks</td>
<td>Usually shorter</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Mortality 20–30% in first episode</td>
<td>Good</td>
</tr>
<tr>
<td>Pathologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epidermal changes</td>
<td>Vacuolar change of the basal cells with confluent necrosis of the entire epidermis</td>
<td>Vacuolar change of the basal cells with numerous necrotic keratinocytes</td>
</tr>
<tr>
<td>Dermal infiltrate</td>
<td>Sparse superficial perivascular lymphohistiocytic</td>
<td>Sparse superficial and deep perivascular lymphohistiocytic, mixed with neutrophils and eosinophils</td>
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between widespread bullous FDE and SJS or TEN. The differentiating clinical and pathologic features are summarized in the Table. Histopathologically, both FDE and EM/SJS/TEN show extensive vacuolar changes in the basal layer and necrosis of keratinocytes, and may be difficult to differentiate from each other [15, 16]. However, the presence of eosinophils, neutrophils, or melanophages in a superficial and deep infiltrate favors FDE over EM/SJS/TEN [15]. In EM/SJS/TEN, the perivascular infiltrate in the dermis is usually only superficial and consists almost entirely of lymphocytes [15]. Eosinophils and neutrophils are usually few if present.

The clinical features and histopathologic findings of Case 1 were consistent with extensive bullous FDE. However, a positive history of prior FDE was lacking and the skin patch test was negative. Case 2 had survived three episodes of almost whole-body bullous drug eruption. The lack of involvement of two mucosal sites and the relatively short and uneventful course favored the diagnosis of TEN-like FDE rather than TEN. Unfortunately, skin biopsy was not performed to confirm the diagnosis.

In summary, these two cases highlight the importance of considering severe bullous FDE in the differential diagnosis of patients with symptoms of SJS or TEN, and the necessity of pathologic study in such cases. The favorable prognosis in these cases supports the notion that TEN-like FDE may be associated with a more favorable prognosis than TEN [1]. However, only a few cases have been reported, and more pathologically proven cases need to be analyzed before a definite conclusion can be reached.

References