Fixed drug eruption: A retrospective study in a single referral center in northern Taiwan

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ABSTRACT

Background/Objective: Fixed drug eruption (FDE) is a dermatosis characterized by recurrent patches or plaques at exactly the same sites with each administration of the causative drug. Vesicles or bullae may sometimes be found, and generalized bullous fixed drug eruption (GBFDE) may be confused with Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN). This study aimed to investigate the clinical and pathologic features of FDE in Taiwan.

Methods: A retrospective analysis evaluated patients with FDE in a referral center in Taiwan covering a period of 11 years. Clinical data, suspected etiologies, and pathology/patch test results were collected. We also compared the GBFDE cases with SJS/TEN overlap or TEN cases to find differentiating clues.

Results: There were 39 FDE patients, including nine GBFDE cases. The most frequent causative drugs were non-steroidal anti-inflammatory drugs (five cases, 12.8%) and antibiotics (four cases, 10.3%). Extremities other than the hands (71.8%) were the most frequently affected sites, followed by the trunk (51.3%), mucosa (38.5%), and hands (33.3%). The average age of FDE patients was 52.2 years (median, 56 years; range, 4–86 years). Patients with GBFDE were significantly older than non-GBFDE patients (69.1 ± 19.7 vs. 47.2 ± 23.6, p = 0.0124) and the trunk was more likely to be involved in GBFDE cases (88.9% vs. 40.0%, p = 0.0197). GBFDE cases also showed tendency to have more mucosal involvement (66.7% vs. 30.0%, p = 0.0631). Although similar to SJS/TEN, GBFDE cases had fewer constitutional symptoms, less mucosal involvement but had previous episodes. Histopathologically, the presence of more than two aggregated dyskeratotic keratinocytes (fire flag sign) in the epidermis was more frequently observed in SJS/TEN, whereas GBFDE had superficial and deep dermal infiltration of eosinophils and melanophages.

Conclusion: FDE is one of the specialized cutaneous drug reactions and GBFDE should be kept in mind and differentiated from SJS/TEN.

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Introduction

Fixed drug eruptions (FDEs) are defined as recurrent lesions at the same skin or mucosal sites after repeated intake of the causative agent.1 FDEs usually present as itching or burning, well-circumscribed, erythematous macules, patches, or plaques that leave hyperpigmentation after resolving. Vesicles or bullae may occasionally be seen. There are many causative agents and the incidence of FDE for a particular drug depends on the frequency of its use. Therefore, the list of etiologic drugs varies from one place to another and from time to time.2

Generalized bullous fixed drug eruption (GBFDE) may be confused with toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome (SJS). The present study aimed to investigate the clinical and pathologic features of FDE in Taiwan and identify several differentiating features between GBFDE and non-GBFDE, as well as between GBFDE and SJS/TEN.

Methods

Patients

From January 2000 to February 2011, cases with suspected diagnosis of FDE recorded in the patch-testing database or skin pathology database of the Department of Dermatology of the National Taiwan University Hospital in Taipei, Taiwan, were recruited. FDE was diagnosed according to the typical clinical features: erythematous,
bright red or dusky red macules that might evolve into an edematous plaque with residual grayish or slate-colored hyperpigmentation (Figure 1A).\(^3\) GBFDE was defined as typical or nonpigmented FDE lesions with bulla formation involving at least three of the following different anatomic sites: head and neck (including lips), anterior trunk, back, upper limbs, lower limbs, and genitalia (Figure 1B).\(^4\)–\(^7\)

Patch tests were performed according to ICDRG regulations and literature after obtaining informed consent.\(^8\),\(^9\) Due to ethical issues, oral challenge tests were not performed. Clinical data, suspected etiologies, and pathology/patch test results were collected from chart records. Pathology-proved TEN or SJS/TEN overlap patients were diagnosed according to the criteria proposed by the European Registry of Severe Cutaneous Adverse Reactions (EuroSCAR) group.\(^10\) Pathologic features such as superficial or superficial and deep inflammation, basal vacuolization, pigment incontinence, and presence of dyskeratotic (apoptotic) keratinocytes were recorded. Eosinophil and neutrophil numbers were also assessed on a four-point scale (score of 0 indicated no specified cell in the specimen; score 1, < 2 cells in every 400× high power field (HPF); score 2, 2–10 cells in one HPF; and score 3, > 10 cells in one HPF).

**Statistical analysis**

Two-sided Wilcoxon rank sum test was used to compare the age difference of GBFDE and non-GBFDE patients. Chi-square tests or Fisher’s exact tests were conducted to compare differences in sex, frequency of previous events, and lesion locations between the two groups. All of the statistical analyses were performed using the SAS software (ver. 9.1.3, SAS Institute, Cary, NC, USA).

**Results**

**FDE patients, including GBFDE and non-GBFDE**

Of the 39 FDE patients recruited in this study, 30 were non-GBFDE and nine were GBFDE patients (Table 1). The average age of FDE patients was 52.2 ± 24.4 years (median, 56 years; range, 4–86 years). The average and median ages of non-GBFDE were younger than those of GBFDE (47.2 ± 23.6 vs. 69.1 ± 19.7 years, \(p = 0.0124\) and 46 vs. 74 years). There was no significant sex preference, although a trend of male predominance was noted (22 men and 17 women). A total of 20 of the 39 FDE patients (51.3%) had previous events, including 14 (46.7%) non-GBFDE and six (66.7%) GBFDE (\(p = 0.4506\)).

Fifteen FDE patients (38.5%) had mucosal involvement. GBFDE cases seemed more likely to have mucosal lesions (66.7% vs. non-GBFDE 30.0%, \(p = 0.0631\)). GBFDE patients were also more likely to have trunk involvement (88.9% in GBFDE vs. 40.0% in non-GBFDE, \(p = 0.0197\)). These results are shown in Table 1.

**Etiologic agents**

Nonsteroidal anti-inflammatory drugs (NSAIDs) were the most common causative agents, accounting for 12.8% of cases (five cases, including four non-GBFDE and one GBFDE). Four cases (10.3%) were caused by antibiotics (one non-GBFDE and three GBFDE). Other cases were caused by miscellaneous agents, including computed tomography contrast and unknown Chinese herbal drugs (Table 2). During this period, only 12 of the 39 patients received patch testing for the suspected causative agents on the previous lesion sites, four (33.3%) of whom had a positive reaction to the suspected drugs.

**GBFDE and TEN**

Four TEN patients and two SJS/TEN overlap patients were included for comparison with GBFDE patients (Table 3). The GBFDE patients were older than the SJS/TEN overlap or TEN patients (69.1 ± 19.7 vs. 58.7 ± 26.1 years; median, 74 vs. 57.5 years). Previous events were noted in six GBFDE patients (66.7%) but none in the SJS/TEN overlap or TEN patients. There was mucosal involvement in six GBFDE

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**Table 1** Demographic data of patients with non-GBFDE and GBFDE.

<table>
<thead>
<tr>
<th></th>
<th>Total (%)</th>
<th>Non-GBFDE (%)</th>
<th>GBFDE (%)</th>
<th>(p) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>39</td>
<td>30</td>
<td>9</td>
<td>NA</td>
</tr>
<tr>
<td>Age (mean ± SD), y</td>
<td>52.2 ± 24.4</td>
<td>47.2 ± 23.6</td>
<td>69.1 ± 19.7</td>
<td>0.0124</td>
</tr>
<tr>
<td>Median age</td>
<td>56</td>
<td>46</td>
<td>74</td>
<td>NA</td>
</tr>
<tr>
<td>Sex (W/M)</td>
<td>17/22</td>
<td>14/16</td>
<td>3/6</td>
<td>0.7042</td>
</tr>
<tr>
<td>Previous events</td>
<td>20 (51.3)%</td>
<td>14 (46.7)%</td>
<td>6 (66.7)</td>
<td>0.4506</td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucosal involvement</td>
<td>15 (38.5)%</td>
<td>9 (30.0)%</td>
<td>6 (66.7)</td>
<td>0.0631</td>
</tr>
<tr>
<td>Lip or oral mucosa</td>
<td>12 (30.8)%</td>
<td>8 (26.7)</td>
<td>4 (44.4)</td>
<td>0.4161</td>
</tr>
<tr>
<td>Genital area</td>
<td>8 (20.5)%</td>
<td>5 (16.67)</td>
<td>3 (33.3)</td>
<td>0.3548</td>
</tr>
<tr>
<td>Extremities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hands</td>
<td>13 (33.3)%</td>
<td>9 (30.0)</td>
<td>4 (44.4)</td>
<td>0.4472</td>
</tr>
<tr>
<td>Other extremities</td>
<td>28 (71.8)%</td>
<td>20 (66.7)</td>
<td>8 (88.9)</td>
<td>0.3994</td>
</tr>
<tr>
<td>Trunk</td>
<td>20 (51.3)%</td>
<td>12 (40.0)</td>
<td>8 (88.9)</td>
<td>0.0197</td>
</tr>
<tr>
<td>Face</td>
<td>6 (15.4)%</td>
<td>3 (10.0)</td>
<td>3 (33.3)</td>
<td>0.1225</td>
</tr>
<tr>
<td>Patch test (+/−)</td>
<td>4/8</td>
<td>3/5</td>
<td>1/3</td>
<td>NA</td>
</tr>
</tbody>
</table>

GBFDE – generalized bullous fixed drug eruption; NA – not applicable; SD – standard deviation.
Comparison of clinical and pathologic features GBFDE and SJS/TEN overlap

Table 3 showed superficial epidermal necrosis in GBFDE and SJS/TEN overlap or TEN patients, respectively. Twenty and six histologic specimens were available for comparison of histopathologic features between GBFDE and SJS/TEN. Seven and six histologic specimens were taken from the perilesional skin or early stage lesions were used for comparison of histopathologic features between GBFDE and SJS/TEN overlap or TEN patients. Constitutional symptoms (e.g. fever, chills, or malaise) were more common in SJS/TEN overlap or TEN patients [three patients (50%) vs. one in GBFDE (11.1%)].

To avoid examining secondary changes of skin pathology due to blister formation or epidermal necrosis, only biopsy specimens taken from the perilesional skin or early stage lesions were used for comparison of histopathologic features between GBFDE and SJS/TEN. Seven and six histologic specimens were available for evaluation in GBFDE and SJS/TEN overlap or TEN patients, respectively. The pathologic features of SJS/TEN overlap or TEN patients showed superficial perivascular inflammation (100%), basal vaculization (100%), presence of fire flag sign (more than two aggregated dyskeratotic keratinocytes, 100%), less pigment incontinence (33.3%), and lower eosinophil score (0–1). These results are shown in Figure 2A and B.

Table 2 Suspected etiologies of FDE.

<table>
<thead>
<tr>
<th>Etiology</th>
<th>GBFDE (n = 9)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs</td>
<td>4 (mefenamic acid, sulindac, piroxicam, acemetacin)</td>
<td>1 (ibuprofen)</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>1 (cephalosporin)</td>
<td>3 (cefixime, cefpime, tetracycline)</td>
</tr>
<tr>
<td>Other drugs</td>
<td>6 (ciprofloxacin, levasiolide, allopurinol, Andrographis paniculata, dicyclomine or mepenzolate)</td>
<td>1 (allopurinol)</td>
</tr>
<tr>
<td>Multiple drugs</td>
<td>7 (doxycycline, acetaminophen, sulfamethoxazole and trimethoprim, dicloxacillin, sulfamethoxazole and trimethoprim, ceftriaxone, clindamycin, levasiolide, allopurinol, colchicine, allopurinol)</td>
<td>2 (sulindac, cimetidine, calcium carbonate, amoxicillin, hydroxyzine, mefenamic acid)</td>
</tr>
<tr>
<td>Other etiologies</td>
<td>5 (computed tomography contrast, unknown Chinese herbal drugs, drug for headache, drugs for upper respiratory tract infection (two cases))</td>
<td>0</td>
</tr>
<tr>
<td>Unknown</td>
<td>7</td>
<td>2</td>
</tr>
</tbody>
</table>

FDE = fixed-drug eruption; GBFDE = generalized bullous fixed drug eruption; NSAID = nonsteroidal anti-inflammatory drug.

Discussion

This study collected 39 cases of FDE from a referral center in northern Taiwan. NSAIDs and antibiotics are the most common drugs causing FDE among many other etiologies. Patients with GBFDE are older and have higher chances of trunk and mucosal involvement than non-GBFDE patients. Patients with GBFDE are also more likely to have previous events but less likely to have constitutional symptoms than patients with SJS/TEN overlap or TEN. The presence of eosinophils and pigment incontinence with absent fire flag sign is an important clue to differentiate GBFDE from SJS/TEN.

By contrast, GBFDE specimens showed no aggregated dyskeratotic keratinocytes in the epidermis (fire flag sign) (0%), frequent pigment incontinence (100%), more common superficial and deep perivascular inflammation (28.6%), and higher eosinophil scores (1–2). These results are shown in Figure 2C and D. Such results indicated that detailed histopathologic examination from early stage lesions or perilesional skin, along with clinical information of previous episodes, constitutional symptoms, and mucosal involvement, were useful in differentiating GBFDE from SJS/TEN.

Although the first case of FDE was described by Bourns in 1889, the term FDE was first proposed in 1894 by Brocq to describe a special type of reaction to antipyrine. The phenomenon of lesions recurring at the previous involved sites has intrigued many dermatologists. Intraepidermal CD8+ T cells with effector-memory phenotype resident in FDE lesions are considered very important in the disease pathogenesis. FDE predisposing sites (i.e. lips, genital areas, or hands) are frequent regions of herpes simplex virus (HSV) reactivation. Previous studies have found that the vast majority of FDE patients are asymptomatic HSV seropositive individuals and their anti-HSV immunoglobulin G (IgG) titers are much higher than in patients with HSV recurrences. FDE lesions found at previously traumatized sites, such as burn scars and insect bites, were also well documented. Moreover, these T cells are found at the site of repeated pathogen entry, such as the lungs. Thus, intraepidermal CD8+ T cells with an effector-memory phenotype resident in FDE lesions may mediate protective immunity. Additional recruitment of other inflammatory cells occurs in the late stage of the disease, and then disease activity is downregulated by regulatory T cells.

A recent French study recruited 59 cases from 17 hospitals over three years, which indicate that FDE is not a common cutaneous adverse drug reaction (roughly one case per year per hospital). However, FDEs are the most frequent cutaneous reactions...
in one report from India, accounting for 30% of all cutaneous adverse drug reactions (61 cases over a 10-year study). There were a total of 39 cases over an 11-year period in one referral center for drug eruption and patch testing in northern Taiwan. It seems that the incidence rate of FDE in Taiwan is similar to that of India. There may be some evidence of genetic predisposition to FDEs.1 The average age of the patients in the current study is 52.2 years, which is older than those of previous reported series (around the fourth decade).18 However, the median age of one recent study (58 years) is close to the present findings.16 The average age of GBFDE patients is higher than those of non-GBFDE patients. This may be explained by the fact that GBFDE patients have more previous episodes than non-GBFDE patients, even though the difference is not statistically significant. It is possible that some patients may overlook or forget prior episodes.

Some studies, including the present one, show a trend toward a male predominance,2 although female predominance has also been reported.16 In the present study, extremities (not including hands)(71.8%) were the most frequently affected sites, followed by trunk (53.3%), mucosa (38.5%), and hands (33.3%). In a study of site involvement in FDE from 105 patients from Turkey, genital mucosa (50.5%) was the most frequently involved site, followed by the trunk (38.1%), lips (37.1%), and hands (32.4%).20 However, some studies show that the lips are the most frequently affected site.18,19,21

The etiology of FDE varies depending on the drugs in vogue at the time in different regions.2 The list of causative drugs is long, including non-narcotic analgesics, antibacterial agents, antifungal agents, antipsychotics, other miscellaneous drugs, and even ultraviolet radiation, emotional and psychiatric factors, heat, menstrual abnormalities, pregnancy, fatigue, cold, and undue effort.2 There is even one report describing a male patient with postcoital FDE after his wife took the causative drug trimethoprim/sulfamethoxazole.22

In the present study, the etiologies are diverse. It is very common that patients take several drugs at one time and, in this study, nine patients took multiple possible drugs. Therefore, it is difficult to identify the true etiology. Furthermore, it is difficult to pinpoint a culprit drug in subsequent episodes considering cross- and polysensitivity.2 Verbov23 reported a case of FDE caused by paracetamol-chlormezanone combination, but not by either drug alone. Drug interactions may lead to formation of chemicals causing FDE. Although oral challenge with subtherapeutic dose remains the most reliable method for defining the etiology, it may cause severe flare-up reactions. Thus, only patch tests were done on the previously involved sites in this study.

Because there is no clear definition of GBFDE in the literature, we proposed that it should fulfill the description of typical FDE or nonpigmented lesions and have at least bullae involving at least three of the following different anatomic sites: head and neck (including the lips), anterior trunk, back, upper limbs, lower limbs, and genitalia.4–7 GBFDE is sometimes confused with SJS/TEN.12 There have been reports of patients surviving from recurrent TEN episodes but such cases are rare. Some authors even suspect that some of these cases are actually GBFDE rather than TEN.12

The present study shows that GBFDE patients are older than SJS/TEN patients and may have previous episodes. Mucosal involvement and constitutional symptoms are less frequent. Commonly incriminated drugs for bullous FDE are rifampicin, metronidazole, paracetamol, paclitaxel, vinbubrine, erythromycin, and ibuprofen.2 This study showed antibiotics (three cases) are the most frequent causative drugs in GBFDE. Histopathologically, FDE and SJS/TEN both showed basal vacuolization and dyskeratosis. However, the presence of eosinophils, neutrophils, or melanophages in the superficial and deep infiltrates favors GBFDE over SJS/TEN.12 The absence of fire flag sign and higher eosinophil scores further
differentiate FDE from SJS/TEN. Unfortunately, because of the limited number of cases, further investigations are warranted.

In conclusion, NSAIDs and antibiotics are the most frequent causative drugs of FDEs in Taiwan. Patients with GBFDE, have more involvement of the trunk, and are easily misdiagnosed as TEN. They are less likely to have constitutional symptoms and mucosal involvement, and may have previous episodes. Skin biopsy is important because the absence of fire flag sign and eosinophils and melanophages in the superficial and deep infiltration favors GBFDE. Detailed histopathologic examination from early stage lesions or perilesional skin, along with clinical information of previous episode, constitutional symptoms and mucosal involvement, will be useful in differentiating GBFDE from SJS/TEN.

Acknowledgments

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References