DERMATOLOGICA SINICA 30 (2012) 11–15

Contents lists available at SciVerse ScienceDirect

Dermatologica Sinica

journal homepage: http://www.derm-sinica.com

ORIGINAL ARTICLE

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

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ARTICLE INFO

Article history:
Received: Jul 19, 2011
Revised: Oct 4, 2011
Accepted: Feb 9, 2012

Keywords:
generalized bullous fixed drug eruption
fixed drug eruption
Stevens-Johnson syndrome
toxic epidermal necrolysis

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.

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,

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doi:10.1016/j.dsi.2012.02.002

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 in the same period were included to compare with GBFDE patients. These 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).

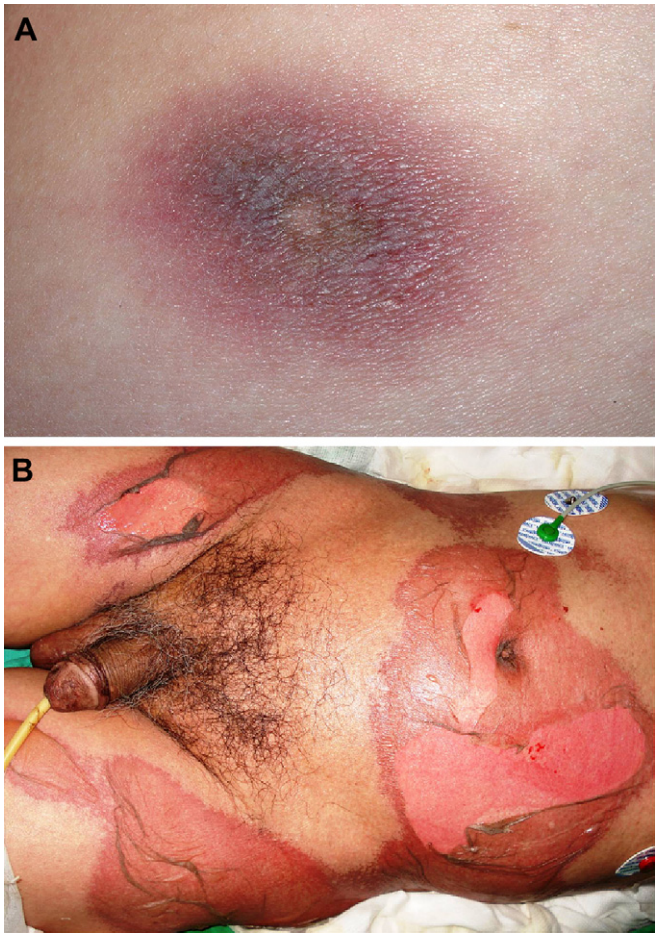

Figure 1 (A) Fixed drug eruption: round erythematous plaque with central dusky red to grayish hyper-pigmentation; (B) generalized bullous fixed drug eruption: large areas of flaccid blisters or erosions involving the abdomen, thighs, and glans penis.

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 cases (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 of 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

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

	Total (%)	Non-GBFDE (%)	GBFDE (%)	*p* value
Number	39	30	9	NA
Age (mean ± SD), y	52.2 ± 24.4	47.2 ± 23.6	69.1 ± 19.7	0.0124
Median age	56	46	74	NA
Sex (W/M)	17/22	14/16	3/6	0.7042
Previous events	20 (51.3)	14 (46.7)	6 (66.7)	0.4506
Location				
Mucosal involvement	15 (38.5)	9 (30.0)	6 (66.67)	0.0631
Lip or oral mucosa	12 (30.8)	8 (26.7)	4 (44.4)	0.4161
Genital area	8 (20.5)	5 (16.67)	3 (33.33)	0.3548
Extremities				
Hands	13 (33.3)	9 (30.0)	4 (44.4)	0.4472
Other extremities	28 (71.8)	20 (66.7)	8 (88.89)	0.3994
Trunk	20 (51.3)	12 (40.0)	8 (88.89)	0.0197
Face	6 (15.4)	3 (10.0)	3 (33.3)	0.1225
Patch test (+/−)	4/8	3/5	1/3	NA

GBFDE = generalized bullous fixed drug eruption; NA = not applicable; SD = standard deviation.