Drug-induced exanthems: Correlation of allergy testing with histologic diagnosis

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Background: Skin biopsies are commonly performed to confirm drug-induced exanthem (DIE). However, the relevance of histologic examination in discriminating between DIE and non-DIE (NDIE) is controversial.

Objective: A retrospective analysis was performed to evaluate the reliability of histologic diagnosis of DIE.

Methods: In all, 91 patients with a skin biopsy specimen of an acute exanthem temporally related to a single identifiable drug underwent complete allergy testing. Their biopsy specimens were retrospectively re-evaluated by 2 dermatopathologists blinded to the original reports to test for discrimination between DIE versus NDIE.

Results: In 35 patients, non-IgE-mediated drug allergy was confirmed by allergy testing, whereas in 56 patients drug hypersensitivity could be excluded. Sensitivity of pathology reports for diagnosis of DIE reached 62.9% with a positive predictive value of 40.7%. Specificity was 41.1% with a negative predictive value of 69.7%. No significant difference in tissue eosinophilia was detected between DIE and NDIE.

Limitations: This was a retrospective study.

Conclusions: Dermatopathologic evaluation of skin biopsy specimens is of limited use in differentiating between DIE and NDIE. All efforts should be made to subject these patients to thorough allergy testing for definitely confirming or ruling out drug hypersensitivity. (J Am Acad Dermatol 2013;69:721-8.)

Key words: challenge testing; drug allergy; drug eruption; drug rash; drug reaction; eosinophils; exanthem; histopathology; provocation testing; skin testing.

Morbilliform exanthems are the most common clinical manifestation of non-IgE-mediated allergic drug hypersensitivity.[1] When the patient is taking a newly prescribed drug, the cause of an acute exanthem is regularly attributed to a cutaneous drug reaction by both patients and physicians. For confirmation of suspected drug-induced exanthem (DIE) some dermatologists recommend a skin biopsy at initial presentation although its significance is debated controversially.[2] Although there have been several attempts to establish histologic criteria for DIE,[3-5] some dermatopathologists emphasize that DIE may not be reliably differentiated from non-DIE (NDIE).[6] Others, however, believe that clinical information and concurrence of several dermatopathological findings may be "strongly suggestive" for DIE.[5]

Abbreviations used:

DIE:	drug-induced exanthem
LTT:	lymphocyte transformation test
NDIE:	non-drug-induced exanthem

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Among the numerous differential diagnoses for acute exanthems, infectious skin reactions are the most important[7] because in case of febrile infectious diseases, antibiotics are generally prescribed and then these drugs are blamed for the exanthem.

The major drawback of previous studies on skin biopsy specimens of drug-associated morbilliform exanthems has been the lack of allergy testing in these patient series.[8] All published histologic studies of drug-associated exanthems merely relied on clinical appearance and course of exanthems as well as temporal correlation of drug intake and onset of skin eruption.[5] However, in recent years we and others have provided compelling evidence of the great discrepancy between clinical suspected diagnosis and results of allergy testing leading to confirmation or exclusion of drug hypersensitivity.[9-19]

CAPSULE SUMMARY

- For confirmation of suspected drug-induced exanthems, skin biopsies are frequently performed.
- Using current histologic methods and criteria, drug-induced exanthems cannot be differentiated from non-drug-induced exanthems.
- This study strengthens the necessity for all patients who may have a drug-associated exanthem to undergo allergy testing to confirm or exclude drug hypersensitivity.

The aim of this retrospective data analysis was to evaluate the reliability of dermatopathological diagnosis of DIE in a cohort of clinically and diagnostically well-defined cases. For this purpose, results of complete allergy testing including skin, in vitro, and provocation testing leading to confirmation or exclusion of DIE was correlated with pathology reports of biopsy specimens obtained from acute morbilliform exanthems.

METHODS

Patients

From 2000 to 2009, all patients referred to our allergy clinic fulfilling the following inclusion criteria were retrospectively identified: (1) a clinical picture and course strongly suggestive of an uncomplicated exanthematous drug reaction; (2) a convincing history implicating a single identifiable drug; (3) a skin biopsy was performed immediately after referral; and (4) the clinical and dermatopathological diagnosis was DIE. The extent of the exanthem was graded as mild (<25% of body surface area), moderate (25%-50% of body surface area), or severe (>50% of body surface area; or erythroderma).[20] Bullous skin reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis were excluded. As part of standard practice in our clinic, all subjects had been informed about any risks and written informed consent for biopsy and allergy testing (skin tests, in vitro tests, provocation testing) had been obtained. This study was approved by the University Hospital of Würzburg Ethics Committee.

Skin testing

We performed prick and intradermal tests on the volar aspect of forearm and patch testing on the upper aspect of the back according to international standards at least 6 weeks after clearance of the exanthematous skin eruption.[21] For prick, intradermal, and patch testing, parenteral drug preparations diluted to nonirritating concentrations according to published data were used. For patch testing Finn Chambers were removed after 1 day and patch, intradermal, and prick test sides were evaluated after 2, 3, and 4 days for late reactions. All agents were freshly reconstituted, and physiologic saline solution was used as negative control.

Laboratory tests

In selected cases with a suspected amoxicillin-induced exanthem, additional laboratory tests were performed. The lymphocyte transformation test (LTT) was performed in 15 patients as described elsewhere.[22]

Provocation testing

Provocation testing was done according to published protocols[23] using standardized doses. General principles of our provocation protocol were: (1) the time interval since the suspected hypersensitivity reaction was at least 6 weeks; (2) during the entire provocation procedure the patient was observed and equipment for emergency treatment was available; (3) the dosage of the drugs was increased stepwise to a normal daily dose with intervals of 1 hour between the individual doses; (4) strict adherence to absolute and relative contraindications for drug provocation tests; and (5) before provocation testing, written informed consent was obtained from each patient.

Histologic analysis

Skin biopsy specimens were taken at the day of referral for diagnosis of DIE as routine standard procedures after having obtained written informed consent. The specimens were processed routinely and stained with hematoxylin/eosin and periodic acid—Schiff. All biopsy specimens had been initially

Table I. Clinical data of 91 patients studied

Age: median (range), y	67 (16-89)
Sex: male/female	28/63
Latency*	
6-12 h	17
1-2 d	43
3-6 d	22
>6 d	9
Exanthema	
Grade 1	10
Grade 2	32
Grade 3	49
Suspected drugs (≥2×)	
Amoxicillin	19
Carbamazepine	11
Allopurinol	6
Diclofenac	5
Sulfamethoxazole	4
Metamizole	4
Clindamycin	3
Hydrochlorothiazide	3
Ampicillin	2
Phenoxymethylpenicillin	2
Acetylsalicylic acid	2
Pantoprazole	2
Nystatin	2

Suspected drugs implicated in only 1 case each: benzylpenicillin, biperiden, bisacodyl, bromazepam, captopril, cefpodoxime, codeine, dimetindene, erythromycin, esomeprazole, ezetimibe, iopromide, itraconazole, loperamide, metoprolol, mezlocillin, midazolam, paracetamol, phenytoin, piroxicam, ramipril, rituximab, sulfasalazine, sumatriptan, tetrazepam, and torasemide.
*Refers to time interval between start of treatment and onset of symptoms.

read by dermatopathologists and had been evaluated as consistent with DIE. For this study, all sections were independently re-read by 2 experienced board-certified dermatopathologists (C. S. S. and C. R.) without information about the history, previous pathology report, or results of allergy testing. Evaluated histologic criteria included features that are either common for the diagnosis of inflammatory skin diseases (pattern analysis; eg, composition, location and density of the inflammatory infiltrate, accompanying parakeratosis), or that have been implicated as discriminating between viral infections (extravasation of erythrocytes) and DIE (apoptotic keratinocytes, eosinophils within the inflammatory infiltrate, papillary edema, and vascular changes).[24] The number of eosinophils within the dermal inflammatory infiltrate was counted in 3 representative fields with ×200 magnification. The number of eosinophils in both groups (DIE vs NDIE) was statistically analyzed. Both dermatopathologists were asked to finally decide between DIE and NDIE, whenever possible.

Table II. Clinical data of 35 patients with non-IgE-mediated drug allergy confirmed by allergologic diagnostics

Age: median (range), y	66 (16-89)
Sex: male/female	13/22
Latency*	
6-12 h	15
1-2 d	14
3-6 d	3
>6 d	3
Exanthema	
Grade 1	0
Grade 2	1
Grade 3	34
Responsible drugs	
Amoxicillin	15
Carbamazepine	10
Sulfamethoxazole	3
Allopurinol	1
Metamizole	1
Captopril	1
Mezlocillin	1
Phenytoin	1
Sulfasalazine	1
Tetrazepam	1

*Latency refers to time interval between start of treatment and onset of symptoms.

Statistical analysis

All histologic parameters of both observers were analyzed separately with Statistica (Statsoft, Hamburg, Germany) using the Mann-Whitney U test; P value less than .05 was considered significant. Comparison of allergy testing and results of pathology reports disregarding ambiguous cases were analyzed using the χ^2 test, P value less than .05 was considered significant. Sensitivity, specificity, negative predictive value, and positive predictive value were calculated using Statistica (Statsoft). For estimation of interobserver agreement the weighted kappa coefficient was determined.

RESULTS

Clinical data

A total of 148 patients with drug-associated morbilliform exanthems were included in this retrospective study and their medical files were reviewed. Of these, 91 could be included in the analysis because in the remaining 57 cases allergy testing was incomplete (eg, provocation testing was refused). The median age of these 91 subjects (63 female and 28 male) at the time of the suspected DIE was 67 years (ranging from 16-89 years). In Table I clinical data including severity of exanthem, latency of the reaction (ie, time interval between start

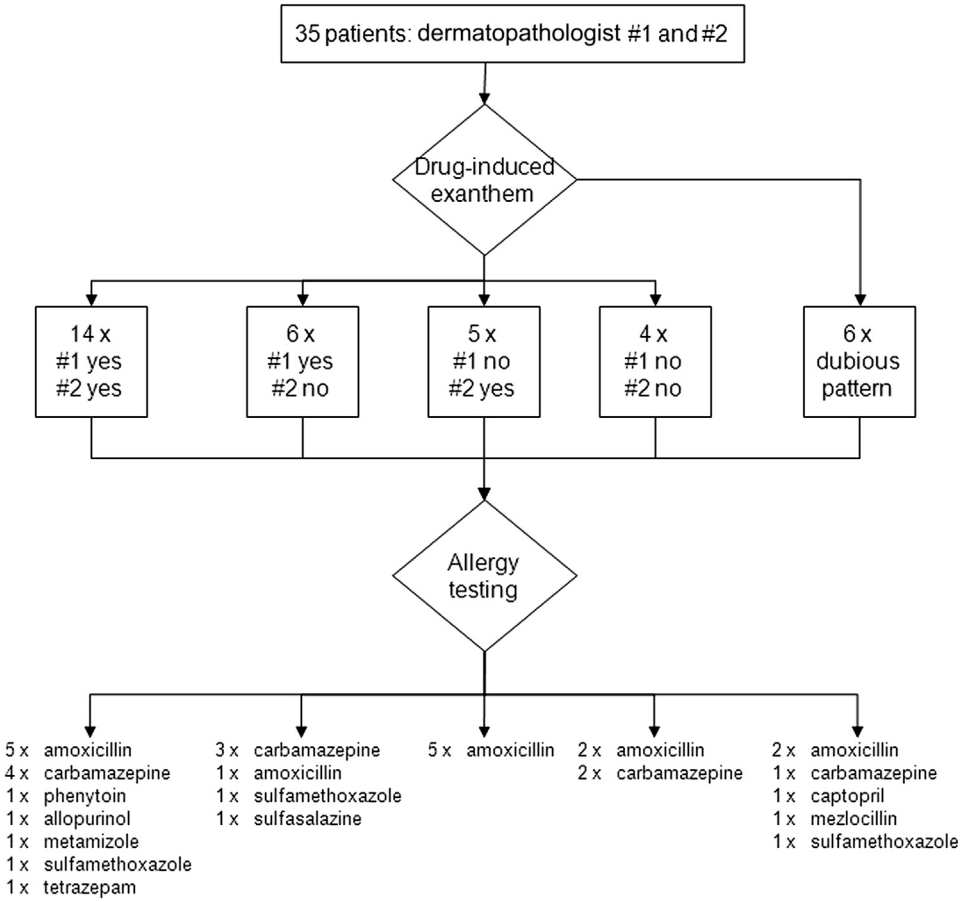

Fig 1. Results of dermatopathologic reports and causative drugs of 35 patients with confirmed drug-induced exanthem. *X*, Times.

of treatment and onset of symptoms), and incriminated drugs are summarized. The time interval between the suspected drug reaction and allergy testing was less than 1 year in 82 cases, in the remaining 9 it was in the range of 1 to 2 years.

Allergy testing

In 56 patients DIE could be excluded by thorough allergy testing. All 56 skin test-negative patients tolerated subsequent provocation testing with the culprit drug. By allergy testing, we identified 35 patients with a definitive diagnosis of non-IgE-mediated drug allergy either by clearly positive skin/laboratory test results or by provocation testing. In 29 cases drug allergy was diagnosed by positive skin test reactions. Eleven patients with amoxicillin allergy had both a positive skin test reaction and a positive LTT result. In 6 patients provocation testing with the culprit drug (once each with tetrazepam, carbamazepine, amoxicillin, captopril, mezlocillin, and sulfamethoxazole) was positive. All exanthematous skin reactions occurring 6 to 12 hours after the last provocation dose were mild and controlled by symptomatic therapy (antihistamines, topical corticosteroids). The clinical data of patients with confirmed drug allergy are summarized in Table II. In 34 of 35 patients with proven drug allergy the exanthem was classified as severe compared with 49 of the total studied 91 patients (Table I). In Fig 1 the 35 patients with proven non-IgE-mediated drug allergy are summarized including results of dermatopathologic reports and the identified causative drugs.

Histologic diagnosis

Table III summarizes the independent histologic findings of the 2 dermatopathologists blinded to the final allergologic diagnosis for both DIE and NDIE, respectively. The most common reaction pattern observed was the combined type of spongiotic and interface pattern (observer 1: 41/observer 2: 27) followed by the perivascular (15/26), spongiotic (10/13), vacuolar interface (6/10), and lichenoid interface pattern (4/5). There was insignificant interobserver disagreement on the histologic pattern. Most importantly, no specific reaction pattern could be significantly attributed to DIE or NDIE. The

Table III. Dermatopathological criteria and results

	Dermatopathologist 1			Dermatopathologist 2		
	Results of allergy testing			Results of allergy testing		
	DIE (n = 35)	NDIE (n = 56)	*P* value	DIE (n = 35)	NDIE (n = 56)	*P* value
Reaction pattern			.1630			.6864
Perivascular	4	11		10	16	
Interface: vacuolar	3	3		3	7	
Interface: lichenoid	1	3		2	3	
Spongiotic	1	9		5	8	
Spongiotic and interface	19	22		10	17	
Neutrophilic	0	0		1	1	
Psoriasiform	2	0		0	0	
Bullous	1	0		2	2	
Ambiguous	4	8		2	2	
Dyskeratosis			.4456			.5088
None	30	43		24	43	
1 +	4	7		10	12	
2 +	0	4		0	0	
3 +	10	2		124	1	
Parakeratosis			.1241			.3482
Yes	7	22		9	21	
No	28	34		26	35	
Epidermal lymphocytic infiltrate			.8672			.7597
None	17	28		12	21	
1 +	16	21		20	31	
2 +	2	7		3	4	
3 +	0	0		0	0	
Dermal lymphocytic infiltrate			.3296			.2551
None	0	1		0	0	
1 +	20	20		23	27	
2 +	11	34		9	27	
3 +	4	1		3	2	
Dermal lymphocytic infiltrate			.3761			.8416
Superficial perivascular	11	22		20	29	
Superficial perivascular/interstitial	12	18		10	22	
Superficial and deep perivascular	5	10		1	0	
Superficial/deep perivascular/interstitial	7	6		4	5	
Papillary edema			.3337			.6303
Yes	8	6		9	11	
No	27	50		26	45	
Vasculitis			.8225			.7784
Yes	1	0		0	2	
No	34	56		35	54	
Blood vessels			.5959			.0867
Normal	3	12		2	7	
Dilated	21	23		17	33	
Dilated: erythrocytes	1	8		1	3	
Dilated: eosinophils, neutrophils	10	13		15	13	
Extravasation of erythrocytes			.4603			.4050
Yes	22	30		23	31	
No	13	26		12	25	

occurrence of dyskeratotic keratinocytes was similar for both conditions. Parakeratosis was present in a slightly but not significant higher proportion of NDIE than DIE. No significant differences in extent of lymphocyte exocytosis or density of the dermal lymphocytic infiltrate were observed. Moreover, there was no significant difference in presence of papillary edema, accompanying vasculitis, or extravasation of erythrocytes. Evaluation of the blood vessels showed no differences in vessel diameter or

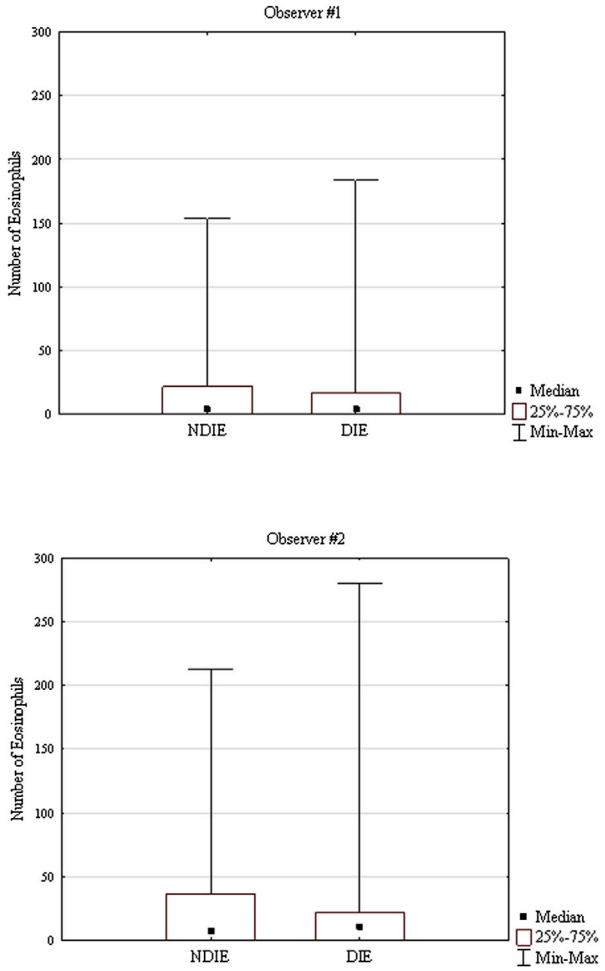

Fig 2. Number of skin eosinophils in drug-induced exanthem (*DIE*) and non-DIE (*NDIE*). Descriptive data analysis and *P* values were determined separately for observers 1 ($P = .8833$) and 2 ($P = .7442$).

intraluminal accumulation of neutrophils. The number of eosinophils within the dermal infiltrate in DIE ranged from 0/0 (observer 1/observer 2) per 3 fields and 184/213 with a mean (± SD) of 21.0 ± 44.8/29.8 ± 49.8. In the NDIE group the number of eosinophils within the dermal infiltrate was between 0/0 and 154/280 with a mean of 19.4 ± 33.5/29.5 ± 60.7. Comparison of DIE and NDIE as shown in Fig 2 did not yield a significant difference in the number of eosinophils within the dermal infiltrate (observer 1: $P = .8833$; observer 2: $P = .7442$).

Correlation of allergy testing and histologic diagnosis

Both sensitivity and specificity as well as positive and negative predictive values of histologic diagnosis of DIE were separately calculated for dermatopathologist 1 and 2 disregarding histologically ambiguous cases (Table IV). From these data, specificity (41.1% vs 35.7%) and negative predictive value (69.7% vs 64.5%) of dermatopathologist 1 were slightly superior to dermatopathologist 2 but these differences did not reach statistical significance ($P = .4051$ vs $P = .6322$). The weighted kappa coefficient (κ_w) measuring the interobserver agreement was 0.2927, confirming only a fair concordance of the 2 dermatopathologists (SE [κ] = 0.0914 and 95% confidence interval [0.1135-0.4719]) (Table V).

DISCUSSION

In clinical practice, morbilliform exanthems developing in temporal relationship with the intake of a specific medication are primarily attributed to drug hypersensitivity. Because of difficulties in differentiating infectious exanthems by morphologic means and because of lack of specific tests, dermatologists may perform skin biopsies in acute patient care to confirm DIE. Our study of a series of patients systematically analyzes sensitivity and specificity of histologic diagnosis of DIE. All previous studies on this topic had the limitation that the diagnosis of DIE was based solely on history, morphology, and clinical course. For the first time to our knowledge, we correlate dermatopathological expert opinion with the results of thorough allergy testing. This approach allows one to reach a definite conclusion on the significance of the histologic diagnosis of DIE. The results regarding sensitivity (62.9%), specificity (41.1%), and positive (40.7%) and negative predictive value (69.7%) of correct diagnosis show that unfortunately no valid conclusions can be drawn from histologic evaluations of skin biopsy specimens.

Several studies have identified drug hypersensitivity in only 15% to 25% of patients with suspected drug reactions referred to a specialized allergy unit.[9-10,12-17,19] Taking into account careful assessment of indications, risks, and limitations, allergy diagnostic procedures are safe and reliable for diagnosis or exclusion of DIE. Step-by-step allergy testing of suspected non-IgE-mediated drug allergy includes skin tests, in vitro tests, and provocation testing. Sensitivity and specificity of skin testing depend on correct test performance and the specific drug investigated. Skin testing with the aminopenicillins ampicillin and amoxicillin is characterized by a high sensitivity; for example, in one of our previous studies, 68 of 71 patients with aminopenicillin allergy showed clearly positive late skin test reactions with either amoxicillin or ampicillin.[12] Falsely positive, ie, irritative skin test reactions caused by frequently tested drugs such as aminopenicillins or carbamazepine are unlikely because of standardized test protocols, control tests with healthy control subjects,

Table IV. Correlation of allergy testing and histologic diagnosis

Dermatopathologist	Sensitivity	Specificity	Negative predictive value	Positive predictive value	*P* value
1	57.1%	41.1%	69.7%	39.2%	.4051
2	62.9%	35.7%	64.5%	40.7%	.6322

Table V. Concordance of pathology reports between dermatopathologists 1 and 2 regarding final diagnosis of drug-induced exanthem versus non-drug-induced exanthem

	Pathology report 1			
	DIE	NDIE	Ambiguous	Sum
Pathology report 2				
DIE	37	14	3	54
NDIE	13	16	2	31
Ambiguous	1	3	2	6
Sum	51	33	7	91

DIE, Drug-induced exanthem; *NDIE*, non-drug-induced exanthem. Weighted kappa (κ_w) = .2927; SE (κ) = 0.0914; 95% confidence interval (0.1135-0.4719).

and many years of experience. Sensitivity and specificity of laboratory tests for non-IgE-mediated allergic hypersensitivity such as LTT also depend primarily on the tested drug. Whereas there are some promising results with aminopenicillins[25] there are limited data on the diagnostic value of LTT regarding other drugs. At this point, LTT can neither replace skin and provocation testing nor be recommended for routine diagnostic purposes.[26]

Despite some limitations, provocation testing remains the gold standard of diagnostic procedures to identify non-IgE-mediated drug allergies.[11,23] A decision for or against a controlled provocation test depends on the degree of the experienced cutaneous drug reaction and the risk for potentially dangerous symptoms such as hepatic and renal involvement, as well as on the anticipated need to re-expose the patient to the drug.[11,23] Furthermore, the possibility of false-negative provocation tests has to be considered; for example, when oral provocation is used, unreliable resorption of a drug may lead to negative results.

Histologic features of morbilliform DIE are generally considered nonspecific: epidermal changes including a mild to moderate interface dermatitis with vacuolization and few dyskeratotic keratinocytes sometimes combined with focal areas of spongiosis.[6,24] The accompanying superficial perivascular infiltrate consists of predominantly lymphocytes with admixture of a variable number of eosinophils. Although "histological changes in exanthematous drug reactions appear non-specific,"[24] some authors consider them "quite characteristic"[24] and thus tremendous efforts in the search for histologic clues of DIE have been undertaken in the past.[3-5,27] In previous studies improvement of clinical symptoms with cessation of the suspected drug has been considered as validation of the histologic diagnosis ignoring the fact that viral exanthems regularly also improve with time.[5] In this context it is not surprising that most dermatopathologists interpret the histologic features in patients with suspected DIE as "suggestive for DIE" or as "compatible with DIE" in their reports.[5] In 1997 Ackerman et al[6] suggested that biopsy specimens of drug eruptions should be signed out with a descriptive diagnosis specifying the histologic pattern with a postscript that differential diagnoses such as exanthematous drug eruption or viral exanthem cannot be differentiated. Nevertheless, less experienced clinicians (especially those not trained in the field of allergy and dermatopathology) not knowing the limits of pathologic interpretation, may still then consider the diagnosis to be "histologically proven" DIE. In these cases an allergy pass incriminating the culprit drug(s) is oftentimes issued without performing allergy testing.

It is still a widespread belief of many clinicians that blood and tissue eosinophilia are typical features of DIE and presence of either one favors DIE over viral exanthem. This issue is of particular importance in clinical scenarios such as bone-marrow recipients in whom a definite distinction of acute graft-versus-host disease and DIE is relevant for prognosis and survival.[28-31] Recently, 3 studies have shown by retrospective quantitative analysis of tissue eosinophilia that the number of eosinophils in skin biopsy specimens of bone-marrow recipients is not predictive for discrimination of DIE from acute graft-versus-host disease.[28-29,31] In our study, we correlate for the first time to our knowledge skin eosinophilia of patients during acute morbilliform exanthems with results of drug allergy testing. We could not detect a significant difference of tissue eosinophilia between DIE and NDIE suggesting that eosinophils within the inflammatory infiltrate of exanthematous skin reactions do not favor a drug pathogenesis over other causes of the exanthem and are of no diagnostic relevance. This issue has been long debated and has been addressed in a variety of

studies in the past.[27,32,33] Nonetheless, in a study measuring peripheral blood eosinophilia in patients with clinical diagnosis of cutaneous drug eruptions (without allergy testing for confirmation of diagnosis) sensitivity was between 18% and 36% (depending on the cut-off level).[33] Skin eosinophilia could be detected in only 24% of cases so the authors concluded that blood and tissue eosinophilia are unreliable diagnostic parameters for clarification whether an exanthem is drug-induced.

In conclusion, history compatible with a DIE and skin biopsy alone leads to an overestimation of non-IgE-mediated allergic drug hypersensitivity. Thorough allergy testing including skin and provocation testing are necessary for definitely confirming or ruling out drug hypersensitivity.

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