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Diagnostics of cutaneous adverse drug reactions: evaluation of patch tests, lymphocyte transformation tests, and drug provocation tests

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Background: Patch tests (PT) and/or lymphocyte transformation tests (LTT) are typically performed, when diagnosed with cutaneous adverse drug reactions (CADR). However, their positivity rates can vary depending on the rash type. Additionally, these tests do not always produce positive results, even when the causative drug is used. Conversely, non-specific reactions can occasionally occur.

Objectives: This study aimed to evaluate the positive rates of PT and LTT for different rash types and to analyze the false-positive and false-negative results of these tests in relation to drug provocation outcomes.

Methods: This was a retrospective descriptive study. The results of PT, LTT, and drug provocation tests for patients diagnosed with CADR at Department of Dermatology, Kyoto Prefectural University of Medicine, from January 2008 to May 2018, were assessed.

Results: A total of 234 patients were diagnosed with CADR, with 43 showing positive reactions to one or more drugs. The highest positivity rate was found in cases of fixed drug eruption. Among the 138 patients who underwent LTT, 44 tested positive for one or more drugs. Drug provocation tests were performed on 31 patients, with 5 exhibiting positive reactions to five drugs. It was observed that three antibiotics produced false-negative results in both PT and LTT. Additionally, antipyretic analgesics yielded false positive results in LTT for 4 patients.

Conclusion: It was suggested that the reactivity of PT and LTT could differ based on the rash type. False negatives and false positives might also happen. These factors should be considered when interpreting the test results.

KEYWORDS

cutaneous adverse drug reactions, drug allergy, drug provocation tests, lymphocyte transformation tests, patch testing

Introduction

Cutaneous adverse drug reactions (CADR) are mucocutaneous lesions caused by either the direct or indirect effects of systemic drugs or their metabolites. These reactions can vary from mild eruptions like maculopapular exanthema to severe, life-threatening conditions such as Stevens–Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms (DRESS) [1, 2]. The underlying pathophysiology of CADR is believed to involve a T-cell–mediated delayed hypersensitivity reaction, which includes four subtypes: Th1-mediated, Th2-mediated, cytotoxic T cell ($CD4^+$ and $CD8^+$)-mediated, and Th17-mediated immune responses [1]. To determine the causative drug in CADR, diagnostic methods such as patch tests (PT), lymphocyte transformation tests (LTT), and oral drug provocation tests are performed.

Drug provocation tests can be risky; thus, many cases initially use minimally invasive procedures like PT and/or LTT. Reports have documented PT results for CADR, suggesting that the positive rate may differ according to the rash type. Additionally, some reactions may be false-negative or false-positive. However, data on patch test results for CADR are limited, and information is scarce. Therefore, this study evaluates the positive rates of PT and LTT for each rash type and investigates potential false-positive and false-negative results based on oral drug provocation test outcomes.

Methods

Data collection

This was a retrospective descriptive study. The results of PT for patients with clinically diagnosed CADR at the Department of Dermatology, Kyoto Prefectural University of Medicine, from January 2008 to May 2018 were gathered. Additionally, the results of LTT and oral drug provocation tests for patch-tested patients were compiled. Data on age, sex, and the type of eruption related to CADR were also recorded. Our protocol received approval from the Ethics Review Board.

Testing methods

PT were prepared using Finn Chambers affixed with Scanpor tape (SmartPractice, Arizona), following the methods used in diagnosing allergic contact dermatitis. The tests were applied to the normal skin of the back and left in place for 48 h. Reactions were read at day 2, day 3, and day 7 [1, 2]. Based on previous reports, a dilution series was prepared. In the absence of specific reports, the substance was diluted with white petrolatum to achieve a weight ratio of 10%–30%. For fixed drug eruptions, PT were performed on both the normal skin of the back and on residual pigmented sites of the eruptions. A positive reaction was defined as (+) or higher according to the International Contact Dermatitis Research Group (ICDRG) criteria. For LTT, a Stimulation Index of ≥180% was considered positive (SRL, Inc., Tokyo, Japan). Drug provocation tests were mostly conducted under hospitalization, starting with one-hundredth or one-tenth of the usual dose, then increasing to one-fifth, one-half, and the full dose if no skin rash occurred. If a skin rash appeared after taking the drug, it was regarded as a positive reaction.

Statistical analysis

This study aimed to gather descriptive data to understand the characteristics of tests used to identify the causative drug in CADR. No statistical comparisons or formal hypothesis testing were performed, so we did not calculate sample sizes.

Results

Drug rash types in patch-tested patients

The study involved 234 patients, including 85 males and 149 females. Their ages ranged from newborn to 87 years old, with a median age of 62. Among them, 43 patients exhibited positive reactions to one or more drugs, while 191 had negative reactions. The most common drug eruption was maculopapular (63%, 146 out of 234 cases), followed by erythema multiforme (12%, 28/234). Other reactions included fixed/urticaria, eczematous, Stevens-Johnson syndrome, psoriasiform, pustular, erythrodermic, lichen planus-like, acute generalized exanthematous pustulosis, and purpuric eruptions. The type of drug eruption could not be determined in 5% (12/234).

Number of patients with positive PT results and positive rates for each rash type

Out of 234 patients with CADR, 43 (18%) showed at least one positive result. The three common clinical types observed in these patients were maculopapular eruptions (26/43 patients), fixed drug eruptions (8/43 patients), and erythema multiforme (5/43 patients). Other types included erythrodermic, lichen planus, and Stevens-Johnson syndrome-type eruptions, each in 1/43 patients, while 2/43 patients were unknown.

Table 1 displays PT positivity rates across different clinical types. Among patients with fixed drug eruption, eight out of 17 (47%) showed positive reactions when PT was applied to the

TABLE 1 The PT positivity rates by clinical types.

Clinical types	Number of positive cases/number of cases undergoing PT	Positive rates
Erythrodermic-type	1/2	50%
Lichen planus-type	1/2	50%
Fixed drug eruption	8/17 0/17	47% (lesional area) 0% (non-lesional area)
Stevens–Johnson syndrome	1/4	25%
Maculopapular type	26/146	18%
Erythema multiforme-type	5/28	18%
Urticarial type	0/8	0%
Eczema-type	0/6	0%
Psoriasis-type	0/3	0%
Pustular type	0/3	0%
Acute generalized exanthematic pustulosis	0/2	0%
Purpura-type	0/1	0%
Unknown	1/11	9%
Total	43/234	18%

TABLE 2 The LTT positivity rates by clinical types.

Clinical type	Number of positive cases/number of cases undergoing LTT	Positive rate
Erythrodermic-type	2/2	100%
Purpura-type	1/1	100%
Urticarial type	3/4	75%
Maculopapular type	33/91	36%
Erythema multiforme-type	4/20	20%
Eczema-type	0/3	0%
Acute generalized exanthemata pustulosis	0/2	0%
Fixed drug eruption	0/2	0%
Lichen planus-type	0/2	0%
Pustular type	0/2	0%
Stevens–Johnson syndrome	0/2	0%
Psoriasis-type	0/1	0%
Unknown	1/6	17%
Total	44/138	32%

lesional area. In contrast, 26/146 patients with maculopapular eruptions (18%) and 5/28 with erythema multiforme (18%) tested positive. Although based on small sample sizes, 1/2 patients with lichen planus or erythrodermic eruptions also exhibited positive reactions.

Positive rates of LTT for each rash type

The study included 138 patients, with 53 males and 85 females, ages ranging from 6 to 87 years and a median age of 66. Among them, 44 exhibited positive reactions, while

TABLE 3 False negative cases of PT and LTT.

	Age/sex	Clinical type	Drug	PT	LTT	Drug provocation test
1	66/M	Maculopapular-type	Amoline®	–	–	+
2	78/M	Maculopapular-type	Sawacillin®	–	–	+
3	67/F	Maculopapular-type	Flomox®	–	–	+

M, male; F, female.

TABLE 4 False positive cases of LTT.

	Age/sex	Clinical type	Drug	PT	LTT	Drug provocation test
1	61/F	Maculopapular-type	PL® Loxonin®	– –	+ +	– –
2	77/F	Maculopapular-type	Loxonin®	–	+	–
3	63/F	Maculopapular-type	Celecox®	–	+	–
4	13/F	Purpuric-type	Calonal®	–	+	–

M, male; F, female.

94 showed negative reactions. The LTT positivity rates according to clinical types are summarized in Table 2. For patients with maculopapular-type eruptions, the positive rate was 36% (33 out of 91). Those with erythema multiforme-type eruptions had a positivity rate of 20% (4 out of 20). All patients with erythrodermic eruptions (2 out of 2) and purpuric eruptions (1 out of 1) tested positive, despite small sample sizes.

Results of drug provocation tests for patients who underwent PT and LTT

The study involved 31 patients, including 10 males and 21 females, aged between 4 and 79 years, with a median age of 50. Five patients exhibited positive reactions to Amolin®, Sawacillin®, Flomox®, Mucodyne®, and Loxonin®. Some patients showed false-negative results for Amolin®, Sawacillin®, and Flomox® in both PT and LTT tests (Table 3). Additionally, false negatives were observed for Loxonin®, Celecox®, and Calonal®. Numerous false-positive results for non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen were also detected on the LTT (Table 4).

Discussion

In this study, we performed PT on 234 patients with CADR. Of those patients, 43 patients showed positive PT results for one or more drugs. The highest positive rate was 47% in patients with fixed drug eruption, where PT was applied directly to the rash area. Next, positive rates were 18% for maculopapular eruptions and 18% for erythema multiforme. Additionally, we carried out LTT on 138 patients who underwent PT, and 44 of them had positive LTT results for one or more drugs. The highest LTT positivity rate, 36%, was observed in patients with maculopapular eruptions. Furthermore, oral drug provocation tests were performed on 31 patients, with 5 showing positive reactions to Amolin®, Sawacillin®, Flomox®, Mucodyne®, and Loxonin®. Notably, three antibiotics produced false-negative results in both PT and LTT, while NSAIDs and acetaminophen caused false-positive LTT results in four cases.

Our research suggests that PT outcomes may differ depending on the clinical type of reaction. According to Thaiwat et al., 44.3% of CADR patients showed at least one positive PT result [3]. Notably, DRESS had the highest positivity at 53.9%, followed by maculopapular rash at 49.0%, and fixed drug eruption at 48.3%. Consistent with our results, fixed drug eruptions tend to have high positive rates. Hassoun-Kheir et al. reported that 32% of CADR patients tested positive on PT, with rates varying by condition: DRESS at 66.6%, morbilliform drug eruption at 38.4%, and erythema multiforme/Stevens-Johnson syndrome at 25% [4]. Since these rates differ across studies, factors such as PT conditions can influence results. Besides the clinical type, the drug concentration used in PT may also affect positivity rates [2]. Furthermore, drug skin tests are typically performed 6 weeks to 6 months after complete healing from the CADR [1, 2]. This study did not collect data on the time between rash resolution and PT so that this interval might have impacted the results.

The results of oral drug provocation tests suggest the presence of false-negative cases for three antibiotics during PT. Lammintausta et al. reported that drug provocation tests

were conducted on 16 patients with positive PT results [5], with 13 of these (81.2%) developing eruptions, while three remained negative. Among skin test negatives, 207 of 229 (90.4%) challenges were negative, and 22 of 229 (9.6%) were positive. PT can yield false-negative results, which may be affected by factors such as low test concentration, differences in solvents, delayed testing after the eruption's acute phase, or the pharmacological characteristics of specific drugs [1, 2, 6]. Moreover, it may be hypothesized that drug eruptions are caused by drug metabolites rather than the initial chemical form. In that case, the PT result will be negative [1, 2, 5]. Conversely, drugs that lead to false positives in PT include irritant-containing substances like sodium lauryl sulfate, along with colchicine and misoprostol [1, 2, 7]. In this study, there were no false positives in cases that underwent drug provocation tests. The cases with negative oral provocation tests were considered unlikely to represent CADR, and their skin symptoms were attributed to other factors such as infections.

In this study, some patients showed false-positive results for NSAIDs and acetaminophen on the LTT. Conversely, false-negative results were observed for three antibiotics on both LTT and PT. The timing of the test may influence these outcomes, as lymphocytes nonspecifically activated *in vivo* during the acute phase may respond [8]. In DRESS patients, positive test results often appear after symptoms have resolved [9]. Furthermore, LTT of drugs such as NSAIDs shows false-positive reactions [10]. When a metabolite acts as an antigen, LTT of the drug shows negative reactions [8]. When steroids, antineoplastic agents, immunosuppressants, or similar drugs are used concurrently, the LTT is more likely to yield a negative result.

This study has several limitations. Notably, the timing of testing and drug concentrations varied among patients, and these factors were not specifically evaluated in our study. In addition, we aimed to perform tests when the doses of systemic corticosteroids or immunosuppressive agents were as low as possible, some cases were tested while these medications were still being administered. This may have affected the test outcomes due to the potential suppressive effects of these drugs. Furthermore, during the study period, the number of patients with DRESS at our institution was extremely small, and PT were not performed in these cases.

In summary, our findings suggest that the diagnostic value of PT and LTT may differ based on the rash type, and both false-positive and false-negative results are possible. These limitations emphasize the need for cautious interpretation in clinical practice. Further research with larger patient groups and standardized protocols is necessary to determine the diagnostic usefulness of these tests more clearly.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Kyoto Prefectural University of Medicine, Ethical Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

RT-M designed the study; TI, RT-M, and KM contributed to data collection; TI, RT-M, NK, and TF wrote the manuscript. All authors contributed to the article and approved the submitted version.

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