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Original Research Article

# Clinical and Histopathological Correlation of Adverse Cutaneous Drug Reactions

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**Abstract:**

**Background and Aim:** Adverse medication reactions are widespread, with the most common being cutaneous symptoms. The incidence of cutaneous medication responses in the hospital ranges from 2% to 3%. The current study sought to investigate the histological aspects of cutaneous adverse drug reactions (ADRs) and their relationship to clinical presentation.

**Material and Methods:** A one-year hospital-based observational study was carried out in the department of dermatology, venereology, and leprology at the Tertiary Care Institute of India on patients presenting with visible cutaneous lesions suspected to be adverse drug reactions and their correlation to histopathological findings. The total sample size was set at 100 patients. All patients underwent a thorough history, physical examination, and standard and relevant investigations. After obtaining informed consent, all patients had biopsies, and histological findings were compared to clinical diagnoses.

**Results:** NSAIDs (37%) were the most common causal agents, followed by amoxycillin (15.0%), fluconazole/itraconazole (9%), ciprofloxacin (5.0%), and cotrimoxazole (7%). (Table 1) Fixed drug eruption (26%) was the most commonly reported lesion, followed by maculopapular rash (20.0%), SJS (11%), urticaria (10.0%), erythema multiforme (8%), AGEP and erythroderma (6%), and TEN (5.0%). Colloid bodies (5.0%), peri appendageal infiltration (6%), interstitial oedema (4%), subepidermal bullae (5.0%), plasma cells (1%), fibrinoid necrosis (1%), intracorneal and subcorneal bullae (4%), were the histological findings observed.

**Conclusion:** Differentiating cutaneous ADR from other inflammatory dermatoses requires the identification of histological patterns and clinical connection. Drug reactions are a clinical problem, therefore clinicopathological correlation can aid in diagnosis.

**Keywords:** Adverse drug reactions, Colloid Bodie, Fixed drug eruption, Maculopapular Rash.



## Introduction

The World Health Organisation (WHO) defines an adverse drug reaction as any undesirable and unplanned drug usage response that occurs at levels commonly used in people for disease prevention, diagnosis, or treatment.[1] Adverse cutaneous medication reactions are common, accounting for 10%-15% of all adverse drug reactions documented.[2] The reported incidence in the hospital context is from 2% to 3% and ranges from mild, self-limiting cases to severe reactions that can cause major morbidity and mortality.[3]

The majority of medication responses are minor and harmless. However, it is critical to diagnose the disease and identify the offending medicine in order to avoid a potentially fatal reaction in the future. Adverse medication reactions aren't limited to the skin; they might affect various organ systems. The severity of adverse cutaneous medication reactions ranges from a minor maculopapular rash to possibly lethal toxic epidermal necrolysis. There are no particular laboratory studies or confirmatory drug testing available to identify the offending substance, and most diagnoses are based solely on clinical judgement.

Maculopapular rash, urticaria, fixed drug eruption (FDE), angioedema, and lichenoid dermatitis are the most common cutaneous adverse drug responses (CADR). Although the majority of CADRs are minor and self-limiting, a few are severe and potentially fatal, such as Stevens Johnson syndrome, toxic epidermal necrolysis, and drug rash with eosinophilia.[4,5] Histological findings in cutaneous adverse drug reactions

(CADR) have been described in several studies, but clinical diagnoses with clear cut criteria have been made only rarely, and many cases lack histological correlation despite being decisive in making the diagnosis, as in acute generalised exanthematous pustulosis (AGEP), SJS, and TEN. To reduce the morbidity associated with CADRs, physicians should have adequate knowledge about the CADRs of medications, which may assist them choose safer drugs, and patients can be trained to prevent re-administration of the offending drug(s).[4,5] With limited medical resources, the cost of ADRs to society and healthcare systems is remarkable, but studies analysing the cost of CADRs are scarce. With these observations in mind, this study was undertaken to assess the clinic-demographic profile of suspected CADR and its correlation to histopathological findings among patients attending the dermatology OPD in a tertiary care hospital in India with the goal of studying the histopathological features of cutaneous

## Material and Methods

A one-year hospital-based observational study was carried out in the department of dermatology, venereology, and leprology at the Tertiary Care Institute of India on patients presenting with visible cutaneous lesions suspected to be adverse drug reactions and their correlation to histopathological findings. The total sample size was set at 100 patients. For baseline data, a prestructured proforma was employed. The current study's inclusion criteria were all age groups and genders presenting with skin and mucosal lesions after drug exposure, patient willingness for examination and procedure, patient willing to give written undersigned consent for biopsy from lesional site, and patients willing to participate in the study. Exclusion criteria for the current study included patients who had a history of taking homoeopathic, ayurvedic, or other indigenous medicines, patients who had cutaneous manifestations due to underlying systemic disease, patients who had cutaneous lesions due to viral exanthems, patients who had a history of accidental or intentional drug abuse, patients who were unwilling to give consent to participate in the study, and patients who did not know the names of medications they were taking.

All patients underwent a thorough history, physical examination, and standard and relevant investigations. After obtaining informed consent, all patients had biopsies, and histological findings were compared to clinical diagnoses.

### Statistical Analysis

The collected data was assembled and input into a spreadsheet programme (Microsoft Excel 2007) before being exported to the data editor page of SPSS version 15 (SPSS Inc., Chicago, Illinois, USA). The confidence level and level of significance for all tests were set at 95% and 5%, respectively.

## Results

The majority of the 100 individuals in the trial were between the ages of 21 and 30, with 25% being between the ages of 41 and 50. The study population included 56 (56.0%) males and 44 (44.0%) females.

NSAIDs (37%) were the most common causal agents, followed by amoxycillin (15.0%), fluconazole/itraconazole (9%), ciprofloxacin (5.0%), and cotrimoxazole (7%). (Table 1) Fixed drug eruption (26%) was the most commonly reported lesion, followed by maculopapular rash (20.0%), SJS (11%), urticaria (10.0%), erythema multiforme (8%), AGEP and erythroderma (6%), and TEN (5.0%). (Table 2)

Colloid bodies (5.0%), periappendageal infiltrate (6%), interstitial oedema (4%), subepidermal bullae (5.0%), plasma cells (1%), fibrinoid necrosis (1%), intracorneal and subcorneal bullae (4%), alternating ortho and parakeratosis (1%), focal acanthosis (3%), spongiosis (14%), extravasation of rbc When we work with clinical and histopathological data, we find a high level of association.

**Table 1: Drugs incriminated in cutaneous adverse drug reactions**

| Drugs | Number | Percentage (%) |
|---|---|---|
| Paracetamol | 15 | 15 |
| Ibuprofen | 12 | 12 |
| Diclofenac | 5 | 5 |
| Nimuselide | 3 | 3 |
| Etoricoxib | 1 | 1 |
| Piroxicam | 1 | 1 |
| Amoxicillin | 15 | 15 |
| Isoniazid | 3 | 3 |
| Rifampicin | 2 | 2 |
| Carbamazepine | 4 | 4 |
| Cefixime | 3 | 3 |
| Ciprofloxacin | 5 | 5 |
| Cotrimoxazole | 7 | 7 |

| | | |
|---|---|---|
| Fluconazole | 9 | 9 |
| Levitrecetatam | 3 | 3 |
| Nitrofurantoin | 3 | 3 |
| Phenytoin | 4 | 4 |
| Steroid | 2 | 2 |
| Tetracycline | 3 | 3 |
| Total | 100 | 100 |

**Table 2: Frequency of pattern of cutaneous adverse drug reactions**

| Diagnosis | Number | Percentage (%) |
|---|---|---|
| Acneform eruption | 3 | 3 |
| AGEP | 6 | 6 |
| Angioedema | 1 | 1 |
| Bullous FDE | 4 | 4 |
| Erythema multiforme | 8 | 8 |
| Erythroderma | 6 | 6 |
| FDE | 26 | 26 |
| Maculopapular rash | 20 | 20 |
| SJS | 11 | 11 |
| TEN | 5 | 5 |
| Urticaria | 10 | 10 |
| Total | 100 | 100 |

## Discussion

Adverse cutaneous drug responses (ACDR) are a substantial cause of morbidity in both hospitalized and outpatients. If severe cutaneous adverse medication reactions are not detected and addressed promptly, the death rate is significant. Several studies have been undertaken over the years to analyze the incidence, clinical manifestations, and common offending medicines.

In our study, the majority of the participants were between the ages of 21 and 30, followed by those between the ages of 31 and 40, which was consistent with a study conducted by Kurle et al, in which the majority of the patients were between the ages of 21 and 40.[6]

There were 56% males and 44% females within the study population, which is consistent with other studies conducted in India for inpatient and outpatient settings, which have demonstrated that males are affected more than females. Kurle et al discovered a male to female ratio of 1:0.63, while Anjaneyan et al discovered a ratio of 1.04:1.[6,7] The male to female ratio in investigations undertaken by Abanti S et al and Patel Raksha M et al was 0.95: 1 and 1.27: 1 respectively.[8,9] Our study's male to female ratio is consistent with that of Patel Raksha M et al, although the little discrepancy from other studies can be due to geographical differences in the study population.[9] In our study, the most commonly reported lesion was fixed drug eruption, followed by maculopapular rash, SJS, Urticaria, erythema multiforme, AGEP, Erythroderma, and TEN, which was similar to the study by Sharma et al, which found fixed drug eruption, maculopapular rash, SJS, Urticaria, erythema multiforme, AGEP, Erythroderma, and TEN. For inpatients, Noel et al. found maculopapular rash as the most common kind of CADR, followed by SJS and FDE.[10] Tejashwani et colleagues discovered that the most common clinical kind of medication reaction was Maculopapular rash.[11] The different clinical manifestations of adverse cutaneous medication reactions in our study are consistent with the findings of Pudukadan et al and Abanti S et al.

The most common causal agents in our analysis were NSAIDs, followed by amoxycillin, fluconazole/itraconazole, ciprofloxacin, and cotrimoxazole. NSAID was the most commonly suspected drug causing cutaneous ADR in a study conducted by Gohel et al.[12] We also discovered that NSAIDS were more usually responsible for fixed drug eruptions, whereas antimicrobials were blamed for maculopapular rash. Phenytoin was the main culprit among anticonvulsants. Cotrimoxazole was the most commonly used offending medicine in the Pudukadan et al study, followed by dapsone, anticonvulsants, and NSAIDs.[13] In the study by Abanti S et al, antibiotics made up 50.9% of the total, with anticonvulsants and NSAIDs accounting for the remaining 11.3%.[14] In the study undertaken by Luciane F F Botelho et al, anticonvulsants were responsible for 23.9% of the reactions, antibiotics were responsible for 22.2%, and 29% of patients were taking multiple drugs.[15] Antibiotics accounted for 50.9% of the total in the study by Saha et al, with anticonvulsants and NSAIDs accounting for 11.3% apiece.[16] The greater occurrence of antimicrobial and NSAIDs in our study can be related to the fact that these medications are frequently recommended

by physicians and general practitioners and are occasionally used irrationally.

The most prevalent histological abnormalities reported in the current investigation were vacuolar interface dermatitis (31.3%), perivascular lymphocytic infiltration (30%), pigment incontinence (18.8%), spongiosis (13.8%), necrotic keratinocytes and eosinophils (8.8%), and RBC extravasation (7.5%). Cupolilo et colleagues found similar results in a research encompassing both indoor and outdoor patients, where the most common histological feature was vacuolar interface dermatitis (41.9%).[17] Weyers et al. and Weinborn et al. determined that there was significant overlap of histological traits.[18,19] As a result, it was frequently difficult to assign particular cases to one of the set of patterns. Our study also found histological overlap, although only a few results were consistently seen in a specific pattern of medication reactions. Pigment incontinence was regularly observed in the majority of cases of fixed drug eruption, associated with scattered necrotic keratinocytes. Clustering of necrotic keratinocytes was seen around acrosyringia in erythema multiforme. SJS/TEN was distinguished from generalised bullous FDE by the presence of subepidermal bullae, clustering of necrotic keratinocytes, and a little perivascular inflammatory infiltration. Histopathological findings were inconclusive in distinguishing AGEP from pustular psoriasis. In cases with erythroderma, generalised characteristics suggestive of vacuolar interface dermatitis were observed, including the presence of eosinophils, perivascular lymphocytic infiltration, and necrotic keratinocytes at all levels of the epidermis, making confirmation difficult. Pearson correlation was used to detect a link between clinical and histological diagnosis using only non-null data, and we observed a strong association with a correlation factor of 0.793 and a T score for correlation coefficient of 10.57. As a result, when we work with clinical and histological data, we can conclude that there is a high association.

The study's limitation was our study had a tiny sample size. A milder form of adverse cutaneous medication reactions mimics some common dermatoses and is misdiagnosed and treated as such.

## Conclusion

Identification of histopathological patterns and clinical correlation is important for distinguishing between cutaneous ADR and the other inflammatory dermatoses. Drug reactions pose clinical challenge thus clinicopathological correlation can help in reaching diagnosis.

## References


1. International drug monitoring: the role of national centres. Report of a WHO meeting. World Health Organ Tech Rep Ser. 1972; 498:1-25. 2.
2. Tian XY, Liu B, Shi H, Zhao ZR, Zhou XP, Zhang T, et al. Incidence of adverse cutaneous drug reactions in 22,866 Chinese in-patients: a prospective study. Arch Dermatol Res. 2015; 307:829-34.
3. Latha S, Choon SE. Incidence of cutaneous adverse drug reactions among medical in-patients of Sultanah Aminah Hospital Johor Bahru. Med J Malaysia. 2017; 72:151---6.
4. Patidar D, Rajput SM, Nirmal PN, Wenny S. Implementation and evaluation of adverse drug reaction monitoring system in a tertiary care teaching hospital in Mumbai, India. Interdiscip Toxcicol. 2013; 6:41-6.
5. Srinivasan R, Ramya G. Adverse drug reactionCausality assessment. IJRPC. 2011; 1:606-12.
6. Kurle DG, Jalgaonkar SV, Daberao VN, Chikhalkar SB, Raut SB. Study of clinical and histopathological pattern, severity, causality and cost analysis in hospitalised patients with cutaneous adverse drug reactions in a tertiary care hospital. Int J Pharm Sci Res. 2018;9(5):1857-64.
7. Anjaneyan G, Gupta R, Vora RV. Clinical study of adverse cutaneous drug reactions at a rural based tertiary care centre in Gujarat. Natl J Physiol Pharm Pharmacol. 2013; 3:129-36.
8. Abanti S, Das NK, Hazra A, Gharami RC, Chowdhury SN,Datta PK. Cutaneous adverse drug reaction profile in a tertiary care outpatient setting in Eastern India. Indian J Pharmacol 2012; 44:792 - 7.
9. Patel Raksha M, Marfatia Y S. Clinical study of cutaneous drug eruption in 200 patients. Indian J Dermatol Venereol Leprol 2008; 74:80.
10. Noel MV, Sushma M, Guido S. Cutaneous adverse drug reactions in hospitalized patients in a tertiary care center. Indian J Pharmacol. 2004; 36:292-5.
11. Tejashwani, Patel D, Bhuptani N. An observational study of cutaneous adverse drug reactions in tertiary hospital. Int J Res Dermatol. 2018; 4:254-8.
12. Gohel D, Bhatt SK, Malhotra S. Evaluation of dermatological adverse drug reaction in the outpatient department of dermatology at a tertiary care hospital. Indian J Pharm Pract. 2014; 7:42-9.
13. Pudukadan D, Thappa DM. Adverse cutaneous drug reactions: Clinical pattern and causative agents in a tertiary care center in South India. Indian J Dermatol Venereal Leprol 2004; 70:20 - 4.

14. Abanti S, Das NK, Hazra A, Gharami RC, Chowdhury SN,Datta PK. Cutaneous adverse drug reaction profile in a tertiary care outpatient setting in Eastern India. Indian J Pharmacol 2012; 44:792 - 7.
15. Luciane F.F. Botelho, Adriana M Porro, Milvia M.S.S.Enokihara, Jane Tomimori. Adverse cutaneous drug reactions in a single quaternary referral hospital. Int J Dermatol. 2016 April: 55(4): e198 - e203.
16. Saha A, Das NK, Hazra A, Gharami RC, Chowdhury SN, Datta PK. Cutaneous adverse drug reaction profile in a tertiary care outpatient setting in Eastern India. Indian J Pharmacol. 2012; 44:792-7.
17. Maria S, Cupolilo N, Wkhlu G, Sdwwhuqv K, Iurp E, Zlwk S, et al. Histological patterns of cutaneous adverse drug reactions. HU Revista, Juiz de. 2009;35(4):296-303.
18. Weyers W, Metze D: Histopathology of drug eruptions -general criteria, common patterns, and differentia diagnosis. Dermatol Pract concept. 2011;1(1):33-47.
19. Weinborn M, Barbaud A, Truchetet F, Beurey P, Germain L, Cribier B. Histopathological study of six types of adverse cutaneous drug reactions using granulysin expression. Int J Dermatol. 2016;55(11):1225-33.