# **Original Research Article**

DOI: https://dx.doi.org/10.18203/issn.2455-4529.IntJResDermatol20221636

# Histopathological and clinical correlation of cutaneous adverse drug reactions

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Received: 30 May 2022 Accepted: 20 June 2022

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#### **ABSTRACT**

**Background:** The aim was to study the histopathological features of cutaneous adverse drug reactions (ADRs) and its correlation to clinical presentation.

**Methods:** We carried our study on 80 patients of drug reactions presented in OPD over a period of 24 months. We noted offending drug, time gap between drug intake and appearance of lesion clinically and performed biopsy to study histopathological patterns and their utility as an aid to diagnosis. WHO-UMC causality assessment method was used in few cases with due diligence. AGEP (acute generalized exanthematous pustulosis) validation score of the EuroSCAR study group was used and SCORTEN for prognosis of SJS/TEN (Stevens-Johnson syndrome/toxic epidermal necrolysis). Histopathological correlation and clinical correlation were statistically analysed.

**Results:** The most common histopathological finding was vacuolar interface dermatitis and presence of eosinophils. The most common drug responsible was antimicrobials. Histopathological findings were most consistent in cases of FDE and AGEP and differentiating viral exanthems from maculopapular rash was challenging. Erythroderma showed varying patterns of histopathology

**Conclusions:** 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.

Keywords: Drug eruption, Histopathology, Skin, Cutaneous

### **INTRODUCTION**

Drug is a chemical substance used in the treatment, cure, prevention, and diagnosis of disease or used to otherwise enhance the physical or mental well-being. They are prescribed with an intention of relieving suffering but sometimes they themselves can cause adverse drug reactions ranging from minor inconvenience to serious organ dysfunction, or even death. Their awareness to the medical world, public and official bodies was highlighted mainly after thalidomide disaster in 1961and since then several worldwide studies have shown ADRs to be a major cause of morbidity and mortality. The clinical

spectrum of cutaneous adverse drug reactions (CADR) is very wide, the common CADRs are maculopapular rash, urticaria, fixed drug eruption (FDE), angioedema and lichenoid dermatitis. Although the majority of CADRs are mild with self-limiting course, few such as Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug rash with eosinophilia are severe and potentially fatal.<sup>2,3</sup>

The histological findings in cutaneous adverse drug reactions (CADR) have been described in several studies, but clinical diagnoses have only rarely been made with clear cut criteria, and many cases lack histological correlation although they are decisive in making the

diagnosis, as in acute generalized exanthematous pustulosis (AGEP), SJS and TEN. It is necessary that the physicians should have adequate knowledge about the CADRs of drugs that may help them in selecting safer drugs and patients can be educated to avoid re-administration of the offending drug(s) to reduce the morbidity associated with CADRs.<sup>2,3</sup>

The cost of ADRs to society and healthcare systems with limited medical resources is remarkable but studies analysing cost of CADRs are scarce, keeping these observations in the background, this study was undertaken to assess the clinicodemographic profile of suspected CADR and its correlation to histopathological findings among the patients attending the dermatology OPD in a tertiary care hospital in Western UP with following aims and objective.

#### **METHODS**

A hospital based observational study was conducted in department of dermatology, venereology and leprology, Muzaffarnagar Medical College, Muzaffarnagar (UP), on patients presenting with visible cutaneous lesions suspected to be adverse drug reactions and its correlation to histopathological findings during 2019-2021. The total sample size was determined to be 80 patients. A prestructured proforma was used for baseline data.

#### Inclusion criteria

Inclusion criteria for current study were all age groups and of either sex presenting with skin and mucosal lesions following exposure to a drug, patient willing for examination and procedure, patient who will give written undersigned consent for biopsy from lesional site, patients willing to become part of study.

## Exclusion criteria

Exclusion criteria for current study were patients presenting with history of intake of homeopathic, ayurvedic and other indigenous medicines, patients presenting with cutaneous manifestations due to underlying systemic disease, patients presenting with cutaneous lesion due to viral exanthems, patients presenting with history of accidental or intentional drug abuse, patient not willing to give consent to be part of study and patients not knowing the name of medications they took.

All patients were selected as per inclusion and exclusion criteria. A detailed history, complete physical examination and routine and appropriate investigations were done for all patients. Biopsy was performed in all patients after taking informed consent and histopathological results were compared with the clinical diagnosis and the statistical analysis was performed by statistical software SPSS version 25.0.

#### **RESULTS**

#### Demographic characteristics

Of study population, comprising of 80 patients, majority of affected patients belonged to 21-30 years (25.3%), and 41-50 years (25.3%). There were 44 (55.0%) males and 36 (55.0%) females among study population.

### Clinical reaction pattern and drugs implicated

Most common causative agents were NSAIDs (37.5%) followed by amoxycillin (15.0%), fluconazole/itraconazole (8.8%), ciprofloxacin (5.0%) and cotrimoxazole (7.5%). Most common lesion reported was Fixed drug eruption (26.3%) followed by maculopapular rash (20.0%), SJS (11.3%), urticaria (10.0%), erythema multiforme (7.5%), AGEP and erythroderma (6.3%), TEN (5.0%).

Table 1: Drugs incriminated in cutaneous adverse drug reactions.

Drugs	N	%
Paracetamol	12	15
Ibuprofen	10	12.5
Diclofenac	4	5
Nimuselide	2	2.5
Etoricoxib	1	1.25
Piroxicam	1	1.25
Amoxicillin	12	15.0
Isoniazid	3	2.5
Rifampicin	2	1.25
Carbamazepine	3	3.8
Cefixime	2	2.5
Ciprofloxacin	4	5.0
Cotrimoxazole	6	7.5
Fluconazole/ Itraconazole	7	8.8
Levitrecetatam	2	2.5
Nitrofurantoin	2	2.5
Phenytoin	3	3.8
Steroid	2	2.5
Tetracycline	2	2.5
Total	80	100.0

# Histopathological diagnosis

The histopathological findings reported were colloid bodies (5.0%), peri appendageal infiltrate (6.3%), interstitial oedema (3.8%), subepidermal bullae (5.0%), plasma cells (1.3%), fibrinoid necrosis (1.3%), intracorneal and sub corneal bullae (3.8%), alternating ortho and parakeratosis (1.3%), focal acanthosis (2.5%), spongiosis (13.8%), extravasation of rbc (7.5%), perivascular lymphocytic infiltrate (31.3%), eosinophils (8.8%), vacuolar degeneration of basal layer (6.3%), pigment incontinence (18.8%), necrotic keratinocytes (11.3%) and vacuolar interface dermatitis (31.3). The offending drug in cases of Maculopapular rash was

NSAIDs among 6, Antibiotics among 7, Anti-fungal among 0, anticonvulsant among 1 and ATT among 2 cases

# Stastical analysis of clinico-histopathological correlation

According the findings of clinical and histopathological data, we have got null hypothesis as the correlation factor which is equivalent to 0.04022 which tend towards the 0. All the findings including the null values is depicted in (Table 4 and 5). But in Table 4, we have incorporated only the non-null data which, depending on which we have found a strong correlation among the data with correlation factor=0.793 which provide us with alternate hypothesis. So with this we can conclude that there is high correlation when we work on clinical and histopathology data. The comparison between the null and alternate hypothesis is shown in (Table 4 and 5).

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

Diagnosis	N	%
Acneform eruption	2	2.5
AGEP	5	6.3
Angioedema	1	1.3
Bullous FDE	3	3.8
Erythema multiforme	6	7.5
Erythroderma	5	6.3
FDE	21	26.3
Maculopapular rash	16	20.0
SJS	9	11.3
TEN	4	5.0
Urticaria	8	10.0
Total	80	100.0

# **DISCUSSION**

In our study, majority of the subjects belonged to 21-30 years (28.0%) age group, followed by 31-40 years (17.3%) of age group, which was in accordance to study conducted by Kurle et al where most of the patients belonged to age group of 21-40 years.<sup>5</sup> There were 55% males and 45% females among study population which is in accordance to most of the studies conducted in India for inpatient and outpatient set up have shown male to be affected more than female like Kurle et al found that the male to female ratio was 1:0.63. and it was 1.04:1 in a study conducted by Anjaneyan et al.<sup>5,6</sup>

In our study, most commonly reported lesion was fixed drug eruption (26.3%) followed by the maculo-papular rash (20.0%), SJS (11.3%), Urticaria (10.0%), erythema multiforme (7.5%), AGEP, Erythroderma (6.3%) and TEN (5.0%) which was similar to the study by Sharma et al, 56 where fixed drug eruption was (34.6%) followed by maculopapular rash and Steven Johnson syndrome

(15.55% each). Noel et al, also reported most common type of CADR as maculopapular Rash followed by SJS and FDE for inpatients.<sup>7</sup> Tejashwani et al found that Maculopapular rash was the most common clinical type of drug reaction (16.66%).<sup>8</sup> In Rahmati-Roodsari's study, the most frequent type of CADR was Maculopapular rash, urticaria and erythroderma.<sup>9</sup> Fixed drug eruption and maculopapular rash were most common pattern in different studies but these little variation in clinical pattern of CADRs could be due to different patterns of drug usage and different ethnic group characteristics within as well as outside the country.

Table 3: Frequency of histopathological findings in cutaneous ADR.

Variables	N	%
Colloid bodies	4	5.0
Periappendageal infiltrate	5	6.3
Interstitial edema	3	3.8
Subepidermal bullae	4	5.0
Plasma cells	1	1.3
Fibrinoid necrosis	1	1.3
Intracorneal and subcorneal bullae	3	3.8
Altrnating ortho and parakeratosis	1	1.3
Focal acanthosis	2	2.5
Spongiosis	11	13.8
Extravasation of RBC	6	7.5
Perivascular lymphocytic infiltrate	24	30.0
Eosinophils	7	8.8
Vacuolar degeneration of basal layer	5	6.3
Pigment incontinence	15	18.8
Necrotic keratinocytes	9	11.3
Vacuolar interface dermatitis	25	31.3

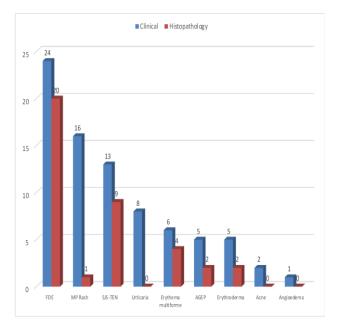


Figure 1: Bar diagram showing corroboration between clinical and histopathological diagnosis of cutaneous ADR.

Table 4: Correlation between clinical and histopathological data (including null values).

Problem	Clinical		Hist	Histopathology	
	N	Population	N	Population	
FDE	24	30	20	26.7	
MP Rash	16	20	1	1.3	
SJS-TEN	13	16.25	9	12	
Urticaria	8	10	0	0	
Erythema	6	7.5	4	5.3	
AGEP	5	6.25	2	2.7	
Erythroderma	5	6.25	2	2.7	
Acne	2	2.5	0	0	
Angioedema	1	1.25	0	0	
Total	80	100	38	50.7	

Table 5: Correlation between clinical and histopathological data (excluding null values).

Type of drug	Clinical		Histopathology		
reaction	N	Population	N	Population	
FDE	24	30	20	26.7	
MP Rash	16	20	1	1.3	
SJS-TEN	13	16.3	9	12	
Erythema Multiforme	6	7.5	4	5.3	
AGEP	5	6.3	2	2.7	
Erythroderma	5	6.3	2	2.7	
Total	69	86.4	38	50.7	

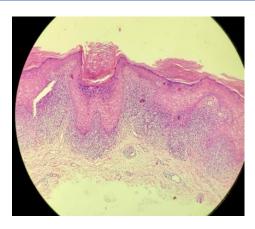


Figure 2: Lichenoid dermatitis: epidermis showing acanthosis and band like dense mononuclear inflammatory infiltrate at dermo-epidermal junction, H&E stain 40X.

In our study, the most common causative agents were NSAIDs (37.5%) followed by amoxycillin (15.0%), fluconazole/itraconazole (8.8%), ciprofloxacin (5.0%) and cotrimoxazole (7.5%). Similar findings were noted in a study done by Gohel et al where NSAID was commonest suspected drug causing cutaneous ADR. <sup>10</sup> We also noted that fixed drug eruptions were more commonly caused by NSAIDS (50%), whereas antimicrobials (43.8%) were incriminated for maculopapular rash. Among anticonvulsants, phenytoin was major culprit.

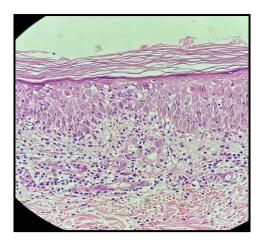


Figure 3: Drug eruption showing spongiosis, necrotic keratinocytes and dermis showing perivascular inflammatory infiltrate comprising of neutrophils, eosinophils and lymphocytes, H&E stain, 400X.

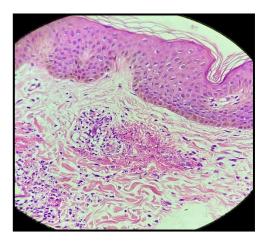


Figure 4: Epidermis lined by stratified squamous epithelium. Underlying dermis shows fibrinoid degeneration and infiltration by nuclear debris of neutrophils around blood vessels, H&E, 400X.

In the study by Modi et al antimicrobials were the common causal drug group followed by NSAIDs and antiepileptics.11 Anjaneyan et al study showed that antimicrobials, NSAIDs, and antiepileptic drugs were most prominent group of drugs responsible for cutaneous ADRs.6 In the study by Saha et al antibiotics constituted 50.9%, followed by anticonvulsants and NSAIDs each constituting 11.3%. 12 The reason for higher incidence of Antimicrobial and NSAIDs in our study can be attributed to the fact that these drugs are commonly prescribed by the physicians and general practitioners and sometimes irrationally used. The integration of National pharmacovigilance program in public health programs (revised National tuberculosis and control program and national AIDS control organization) has increased reporting of ADRs due to antitubercular and antiretroviral drugs, which has been reflected in our study. The slight difference from other studies can be attributed to the relatively poor socio-economic status, prescription pattern and over the counter availability of the drugs.

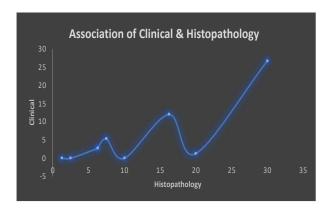


Figure 5: Correlation between clinical and histopathological data (including null values).

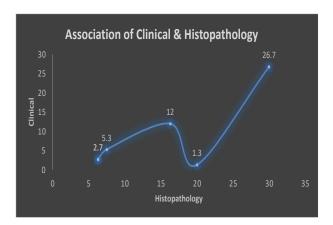


Figure 6: Correlation between clinical and histopathological data (excluding null values).

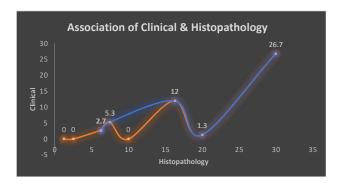


Figure 7: The comparison between the null and alternate hypothesis.

In our study, the most common histopathological findings reported was vacuolar interface dermatitis (31.3%), followed by perivascular lymphocytic infiltrate (30%), pigment incontinence (18.8%), spongiosis (13.8%), necrotic keratinocytes and eosinophils (8.8%), extravasation of RBCs (7.5%). Similar findings were noted in the study conducted by Cupolilo et al involving both indoor and outdoor patients, where the most frequent histopathological pattern was vacuolar interface dermatitis (41.9%). The studies conducted by Weyers et al. and Weinborn et al. concluded that there was marked

overlap of histological features. 14,15 Thus, it was often difficult to attach individual cases to one of the set of patterns. Our study also showed overlap of histopathological findings, but few findings were consistently seen in specific pattern of drug reactions. In most of the cases of fixed drug eruption, pigment incontinence was consistently noticed along with scattered necrotic keratinocytes. In erythema multiforme, clustering of necrotic keratinocytes was noted around acrosyringia. Subepidermal bullae, clustering of necrotic minimal perivascular inflammatory keratinocytes, infiltrate was seen in cases of SJS/TEN which helped in differentiating it from generalized bullous FDE. In the differentiation between AGEP and pustular psoriasis, histopathological findings were of limited help. In cases of erythroderma, generalized features suggestive of vacuolar interface dermatitis, presence of eosinophils and perivascular lymphocytic infiltrate and necrotic keratinocytes at all levels of epidermis were noted, thus making confirmatory diagnosis difficult. Pearson correlation was applied to find correlation between clinical and histopathological diagnosis incorporation of only non- null data, depending on which we found strong correlation among the data with correlation factor of 0.793 and T score for correlation coefficient 10.57. Hence, we can conclude that there is high correlation when we work on clinical and histopathological data.

According the findings of clinical and histopathological data, we have got null hypothesis as the correlation factor which is equivalent to 0.04022 which tend towards the 0. In Figure 5 we have incorporated all the findings including the null values. But in Figure 6 we have incorporated only the non-null data, depending on which we have found a strong correlation among the data with correlation factor=0.793 which provide us with alternate hypothesis. So, with this we can conclude that there is high correlation when we work on clinical and histopathology data in corroboration with each other

#### 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.

Funding: No funding sources Conflict of interest: None declared

Ethical approval: The study was approved by the

institutional ethics committee

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Cite this article as: Singh P, Jaiswal A, Arora K. Histopathological and clinical correlation of cutaneous adverse drug reactions. Int J Res Dermatol 2022;8:392-7.