ORIGINAL ARTICLE

DOI: 10.4274/eamr.galenos.2022.27147
Eur Arch Med Res 2023;39(2):79-83

Maculopapular Drug Eruptions: Diversity of Histopathological Changes

Gamze Kulduk[1], Özben Yalçın[1], Zeynep Betül Erdem[2], Damla Karabıyık Altıok[3], İlteriş Oğuz Topal[4]

[1]*University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital, Clinic of Pathology, İstanbul, Turkey*
[2]*University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Pathology, İstanbul, Turkey*
[3]*Mardin Training and Research Hospital, Clinic of Pathology, Mardin, Turkey*
[4]*University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital, Clinic of Dermatology, İstanbul, Turkey*

Abstract

Objective: Cutaneous adverse drug reactions are commonly seen in dermatology outpatient clinics thereby comprising a large part of the pathology materials. However, the lack of information about drug usage may cause misdiagnosis. The aim of this study was to discuss criteria that may help in recognition of drug eruptions due to histological patterns.

Methods: Ninety-two patients who were diagnosed with maculopapular rash between 2015 and 2018 at the pathology and dermatology departments of our hospital were examined according to distribution of histopathological changes and patterns.

Results: This study was conducted to evaluate histopathological spectrum of eruption which were known to be drug related that cleared following cessation clinically. Hyperkeratosis or parakeratosis was detected in 26.1% (24/92) and 35.9% (33/92) of all cases, respectively. The most common feature in the epidermis was acanthosis in 88 of 92 biopsies (96%) and the least common feature was atrophy in 4 of 92 biopsies (4%). Dermal inflammation was in 89 of 92 cases (97%). Inflammation was mostly consisted of mononuclear cells. Vacuolar interface dermatitis pattern, spongiotic dermatitis pattern, lichenoid dermatitis pattern, or leukocytoclastic vasculitis pattern was detected in 93.5% (86/92); 58.7% (54/92); 16.3% (15/92); 7.6% (7/92) of all cases, respectively.

Conclusion: Accurate diagnoses of drug eruption are important because they may cause patients' annoyance, hospitalization, economic load, and sometimes be fatal. Like Ackerman emphasized drugs elicit diversity of histological changes but none of the reaction pattern are specific.

Keywords: Maculopapular drug eruption, histopathological reaction patterns, cutaneous drug reactions

INTRODUCTION

Cutaneous maculopapular drug reactions (CDR) are commonly seen in dermatology outpatient clinics associated with the usage of a variety of drugs during daily life (1). The clinical spectrum of CDR is broad. Common CDR symptoms are maculopapular rash, urticaria, fixed drug eruption, angioedema, and contact dermatitis. The majority of CDR is a mild self-limited disease. Few such as Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug rash with eosinophilia are severe and potentially fatal (1).

Like clinical manifestation, histopathology of drug eruptions also presents in a wide range. Biopsies can show a variety of inflammatory disease patterns and panniculitis-like changes (2). Ackerman emphasized that drugs can elicit any of the nine basic patterns of inflammatory diseases in the skin, and none of those patterns is specific for a drug eruption (2,3). Therefore diversity of CDRs is an important aspect in both dermatology and pathology clinics. Even though drug eruptions are commonly biopsied, histopathological changes are vague. In the literature, some authors declared that histopathological changes in drug

Address for Correspondence: Zeynep Betül Erdem, University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Pathology, İstanbul, Turkey
Phone: +90 551 428 64 98 **E-mail:** zberdem@gmail.com **ORCID ID:** orcid.org/0000-0002-0019-1922

Cite this article as: Kulduk G, Yalçın Ö, Erdem ZB, Karabıyık Altıok D, Topal İO. Maculopapular Drug Eruptions: Diversity of Histopathological Changes. Eur Arch Med Res 2023;39(2):79-83

Received: 03.04.2022
Accepted: 12.10.2022

eruption are non-specific (3) and some said that histopathological diagnosis can be made only with clinical information (4).

In the following, histopathological findings in 92 cases of maculopapular eruption with proven drug-related (with the resolution of eruption following cessation of the drug) were evaluated. We would like to discuss criteria that may aid the diagnosis of drug eruptions due to histological patterns and hypothesize that the coexistence of dermatosis patterns can be a diagnostic clue. We also conclude that lymphatic dilatation in the upper dermis is a common finding of drug eruptions.

METHODS

Ninety-two patients with maculopapular rash who were diagnosed as drug-related between 2015 and 2018 at the department of pathology were studied. The diagnoses were based on morphology in hematoxylin and eosin (H&E) stained sections and confirmed by the clinic. Clinical information was gathered by using the institutes' database records.

The median age of the patients was 50.58±17.70 years. There were 40 men (43.5%) and 52 women (56.5%). All specimens were punch biopsies. H&E-stained slides were reviewed by two pathologists (GK and ÖY).

Statistical Analysis

For statistical analysis, the NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used. Pearson chi-square test and Fisher's Exact test were used to compare descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) as well as qualitative data. Significance was evaluated at $p<0.05$ levels.

Appropriate research ethics and review board permissions were obtained from the Okmeydanı Training and Research Hospital Institute with the reference number 1291 on 05/14/2019.

RESULTS

Ninety-two cases were evaluated. Hyperkeratosis or parakeratosis was detected in 26.1% (24/92) and 35.9% (33/92) of all cases, respectively (Table 1). The most common feature in the epidermis was acanthosis in 88 of 92 biopsies (96%) and the least seen feature was atrophy in 4 of 92 biopsies (4%) (Table 1). Sixteen cases showed sawtooth acanthosis and 3 cases showed psoriasiform acanthosis. Dermal inflammation was in 89 of 92 cases (97%). Regarding the inflammation, localization was superficial in 88% (81/92) of cases and; was both superficial and deep in 8.7% (8/92) of cases (Figure 1A). No inflammation was observed in 3 cases (3.3%) (Table 1). Inflammation mostly consisted of mononuclear cells, and atypical lymphocytes were not observed, as mentioned in some studies (5). Eosinophils and neutrophils were present in 95.7% and 21.7% of all cases, respectively (Table 1).

Necrotic keratinocytes were detected (both encountered at dermo-epidermal junction and scattered within epidermis) in 48.9% (45/92) of all cases (Table 1). The rates of melanophages, basal hyperpigmentation, erythrocyte extravasation or scale crusts were 10.9% (10/92) and 18.5% (17/92), 33.7% (31/92), 7.6% (7/92) respectively (Table 1).

Lymphatic vessels of the superficial dermis were frequently dilated and lymphatic dilatation was present in 93.5% of cases (Table 1).

The incidence for vacuolar interface dermatitis pattern (VIDP) was 93.5% (86/92), the incidence for spongiotic dermatitis pattern (SDP) was 58.7% (54/92), the incidence for lichenoid dermatitis pattern (LDP) was 16.3% (15/92), and the incidence for leukocytoclastic vasculitis pattern (LCVP), was 7.6% (7/92) (Figure 1B).

We examined the dermatitis patterns due to histopathologic features. The correlation between LDP and melanophages was statistically significant ($p=0.009$; $p<0,01$). The correlation between SDP and basal hyperpigmentation was statistically significant ($p=0.030$; $p<0.05$).

Table 1. Histopathologic changes observed in biopsies

Hyperkeratosis		24 (26.1%)
Parakeratosis		33 (35.9%)
Epidermal changes	Acanthosis Atrophy Psoriasiform acanthosis Sawtooth acanthosis	70 (76.1%) 4 (4.3%) 3 (3.3%) 15 (16.3%)
Inflammation	Absent Superficial Superficial + deep	3 (3.3%) 81 (88.0%) 8 (8.7%)
Eosinophils		88 (95.7%)
Neutrophils		20 (21.7%)
Necrotic keratinocytes		45 (48.9%)
Lymphatic dilatation		86 (93.5%)
Pustule formation		12 (13.0%)
Erythrocyte extravasation		31 (33.7%)
Melanophages		10 (10.9%)
Basal hyperpigmentation		17 (18.5%)
Crust formation		7 (7.6%)
Edema of papillary dermis		9 (9.8%)
Elongation of rete ridges		5 (5.4%)

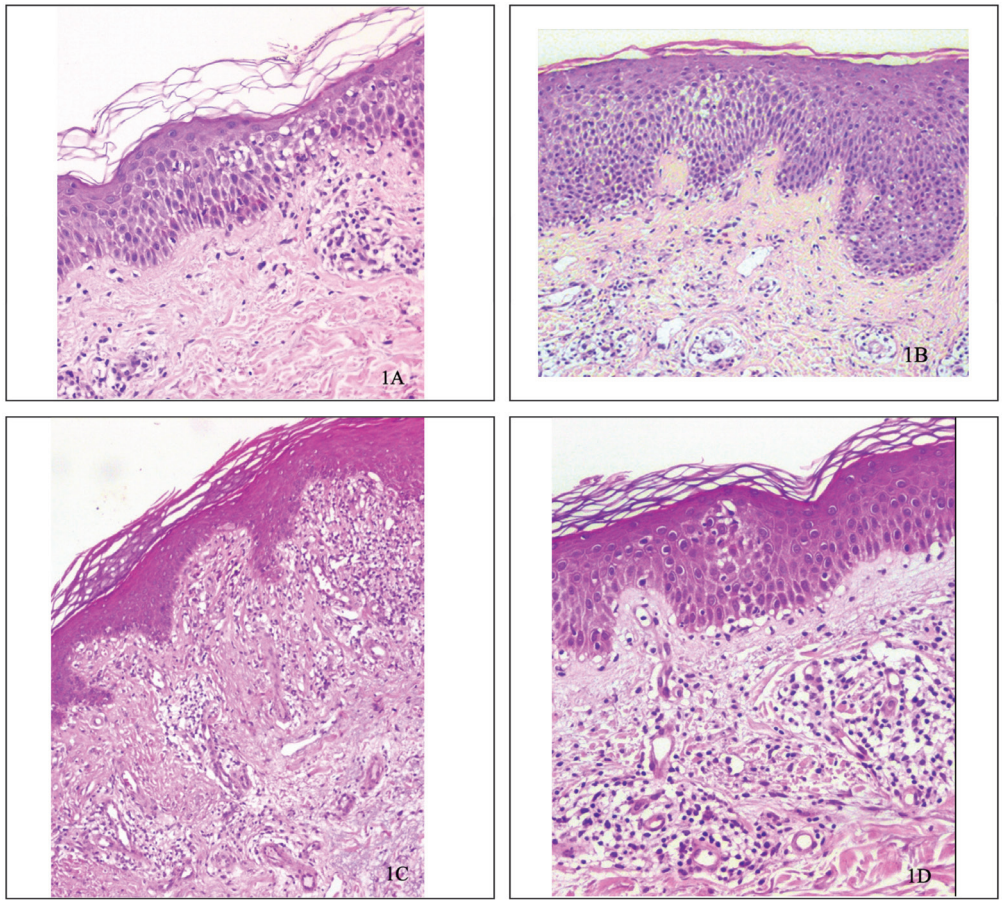

Figure 1. Photomicrographs of selected cases. (A) Basal hyperpigmentation, basket weave hyperkeratosis, spongiosis and vacuolar changes at the dermo-epidermal junction and superficial perivascular inflammation (H&E, x100). (B) Coexistence of VIDP with SDP (H&E, x200). (C) Coexistence of VIDP with LDP (H&E, x100). (D) Combination of VIDP with LCVP and SDP (H&E, x200)

VIDP: Vacuolar interface dermatitis pattern, H&E: Hematoxylin and eosin, LDP: Lichenoid dermatitis pattern, SDP: Spongiotic dermatitis pattern, LCVP: Leukocytoclastic vasculitis pattern

The correlations between VIDP and basal hyperpigmentation, erythrocyte extravasation, melanophages, and lymphatic dilatation were statistically insignificant (p=0.074, p=0.401, p=0.509, p=0.448 respectively). The correlations between SDP and erythrocyte extravasation, melanophages, and lymphatic dilatation were statistically insignificant (p=0.088, p=0.086, p=0.168 respectively).

The correlations between LDP and basal hyperpigmentation, eritrocyte extravasation, and lymphatic dilatation were statistically insignificant (p=0.288, p=0.237, p=0.068, p=0.584, respectively). The correlations between LCVP and basal hyperpigmentation, melanophages, eritrocyte extravasation, and lymphatic dilatation were statistically insignificant (p=0.088, p=0.924 p=0.416, p=0.529, respectively).

Furthermore, coexisting histopathological patterns were examined. Of all cases, one pattern was observed in 29.3% (27/92). Coexistence of two patterns were seen in 62% (57/92) and coexistence of three patterns were seen in 7.6% (7/92) of all drug eruption cases. Regarding the coexistence of patterns, the most common was VIDP with SDP in 55.4% (51/92) (Figure 1B) and VIDP with LDP in 15.2% (14/92) (Figure 1C) of all cases (Table 2).

Table 2. Co-existence of patterns	
VIDP with SDP	51 (55.4%)
VIDP with LDP	14 (15.2%)
VIDP with LCVP	5 (5.4%)
SDP with LDP	5 (5.4%)
SDP with LCVP	3 (3.3%)
VIDP with SDP and LDP	5 (5.4%)
VIDP with SDP and LCVP	2 (2.2%)

VIDP: Vacuolar interface dermatitis pattern, LDP: Lichenoid dermatitis pattern, SDP: Spongiotic dermatitis pattern, LCVP: Leukocytoclastic vasculitis pattern

DISCUSSION

Drug eruptions are the most common disorder of the skin with many morphological features and diagnostic challenges that can resemble other dermatoses. It is crucial to differentiate inflammatory dermatoses from dermatoses like drug eruptions.

Recently it has been stated that a combination of different histopathological patterns indicates a diagnostic clue to drug eruptions (2,6). With this knowledge we would like to evaluate and classify our cases according to their inflammatory reaction patterns, as well as to identify common and overlapping patterns and other accompanying features. Similar to the literature, the most common pattern was VIDP, followed by SDP in our study (2,7,8). Eighty-six of 92 (93.5%) cases showed VIDP pattern as in the study by Naim et al. (7).

To our knowledge, this is the first study submitting data on the coexistence of histological patterns. Our study demonstrated the combination of two or more patterns in 64 of 92 cases (69.5%). Regarding the coexistence of 2 patterns, the most common was VIDP with SDP in 55.4% (51/92) of all cases and the least was SDP with LCVP in 3.3% (3/92). Three of all cases showed a combination of patterns of VIDP, SDP with LCVP (Figure 1D). Psoriasiform or granulomatous patterns are rare forms of drug-related eruptions (6). There were none of these patterns in our cases.

Inflammation is a consistent finding of maculopapular drug eruptions (6,7). According to Naim et al. (7) all cases in their study presented with the inflammatory cells in the dermis. In our study, 3.3% (3/92) of cases were not associated with inflammation (7). Therefore, inflammation is not an indispensable finding for a drug reaction. Our study demonstrated that superficial and deep localized inflammation (8.7%) was lower than the literature (7). Scale crusts were encountered in 7.6% (7/92) of biopsies, unlike the Naim et al. (7) study.

Justiniano et al. (6) stated that the presence of eosinophils is a diagnostic clue. The absence of eosinophils does not rule out drug-related eruptions (6) but drug-related eruptions are often associated with an infiltrate of eosinophils and/or neutrophils (2,8). In our study, eosinophils were present in 88 of 92 cases (95.7%), and neutrophils were present in 20 of 92 cases (21.7%). Naim et al. (7) found eosinophils to be absent in some cases and lower eosinophil counts were detected by other researchers (2,8). Inflammatory infiltrate in dermatoses can also contain eosinophils, therefore accompanying neutrophils to the inflammation can be used as a diagnostic clue.

Melanin incontinence is the result of basal cell damage and observed more frequently in drug or solar damage induced dermatoses (9). Our study showed that the correlation between LDP and melanophages and the correlation between SDP and basal hyperpigmentation was statistically significant. The correlation between LDP with melanophages and the correlation between SDP with basal hyperpigmentation was statistically significant. Therefore, this knowledge can be used when evaluating biopsies taken for drug-related rash.

Naim et al. (7) stated that none of the biopsies showed LCVP contrary to our findings. In our study, 93.5% of biopsy specimens showed lymphatic dilatation in the upper dermis. This was also a common finding in the study by Naim et al. (7).

Similar to the literature, acanthosis was a common finding. In especially irregular acanthosis can be due to some drugs (10).

As a result, we share the same opinion with Weyers and Metze (2), that histopathological diagnosis of drug eruptions can be difficult without clinicopathologic correlation.

CONCLUSION

Drug eruptions are the most common disorder of the skin with many morphological features and diagnostic challenges that can resemble other dermatoses. Histopathological diagnosis of drug eruptions can be difficult without clinicopathologic correlation. However, the coexistence of more than one pattern and lymphatic dilatation can be a diagnostic clue.

Ethics

Ethics Committee Approval: Appropriate research ethics and review board permissions were obtained from the Okmeydanı Training and Research Hospital Institute with the reference number 1291 on 05/14/2019.

Informed Consent: This research project involved the retrospective analysis of archived material (slides) for the purpose of an observational study. No interventional procedures were conducted, and the identities of the patients were protected throughout the study. As a result of the retrospective nature of the study and the use of archive slides with no impact on treatment, informed patient consent was not obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: G.K., Design: G.K., Ö.Y., Z.B.E., D.K.A., İ.O.T., Data Collection or Processing: Z.B.E., D.K.A., Analysis or Interpretation: G.K., Literature Search: G.K., Z.B.E., Writing: G.K., Z.B.E.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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