Original Article

Histopathological Characterization of Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) and Comparison with Maculopapular Drug Rash (MPDR)

Abstract

Introduction: Drug rash with eosinophilia and systemic symptoms (DRESS) is a severe cutaneous adverse drug reaction (cADR) associated with significant systemic involvement and greater mortality. Variable patterns of inflammation are reported in the histopathology of DRESS. However, the role of histopathology in predicting systemic involvement and thus final outcome remains elusive. In the present study, we aim to review clinical and histopathological characteristics of patients with DRESS and compare their histopathology with that of maculopapular drug rash. **Materials and Methods:** A retrospective analysis of cases of cADRs diagnosed from July 2014 to July 2020 at a single tertiary care institute was performed. A RegiSCAR score of ≥4 was used to recruit patients as DRESS. Patients with a probable/definite diagnosis of cADR on the basis of Naranjo criteria and presenting with exanthem attaining a RegiSCAR score of ≤3 were categorized as MPDR. Correlation of histopathology characteristics with the investigative profile of patients with DRESS was done. MPDR and DRESS were also compared for histopathological characteristics using Chi-square test. Further histopathology of patients with drug rash (both DRESS and MPDR) having systemic involvement was compared with those without systemic involvement to identify specific predictors. **Results:** Eighteen patients of DRESS and 20 of MPDR fulfilled the inclusion criteria. Most common drugs implicated were anticonvulsants (27.8%). Characteristic findings seen on histopathology in patients with DRESS were epidermal spongiosis (94.5%), epidermal dyskeratosis (33.3%), lymphocytic exocytosis (88.9%), interface vacuolization (77.8%), papillary dermal edema (100%). and perivascular lymphocytic infiltrate (100%). Findings in favor of DRESS compared to MPDR were lymphocytic exocytosis ($P < 0.001$), interface vacuolization ($P = 0.002$), severe spongiosis ($P = 0.046$), severe papillary dermal edema ($P = 0.018$), and higher density of dermal infiltrate ($P = 0.005$). Lymphocyte exocytosis and distribution and density of dermal inflammatory infiltrate correlated significantly with deranged kidney function. **Conclusion:** Histopathology revealing prominent basal vacuolization, spongiosis, and dense dermal infiltrate suggests DRESS. Lymphocyte exocytosis and distribution and density of dermal inflammatory infiltrate predict renal involvement.

Keywords: *Basal vacuolization, DRESS, maculopapular drug rash*

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Introduction

Drug rash with eosinophilia and systemic symptoms (DRESS) is a severe cutaneous adverse drug reaction (cADR) characterized by a widespread exanthem along with hematological and solid organ abnormalities predominantly affecting liver and kidney.[1] Its incidence varies from 1 in 1,000 to 1 in 10,000 drug exposures with 10% mortality, primarily due to liver failure.[2,3] The initial description of DRESS dates back to 1940, when a.cADR was identified with hydantoin intake typified by rash, fever, lymphadenopathy, and systemic upset. Similar reports with other anticonvulsants led to the terminology, anticonvulsants hypersensitivity syndrome.[2] But with the description of other drugs causing similar presentation, various names including drug-induced hypersensitivity syndrome and drug-induced delayed multi-organ hypersensitivity syndrome were used. DRESS, however, appears to be a commonly used terminology now. Though clinico-investigative literature on DRESS is plentiful, histopathological description is scarce. After the initial histopathological description of DRESS as drug-induced

How to cite this article: Jindal R, Chugh R, Chauhan P, Shirazi N, Bisht YS. Histopathological characterization of drug rash with eosinophilia and systemic symptoms (DRESS) and comparison with maculopapular drug rash (MPDR). Indian Dermatol Online J 2022;13:32-9.

Received: 15-Jul-2021. **Revised:** 05-Aug-2021. **Accepted:** 20-Aug-2021. **Published:** 24-Jan-2022.

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Access this article online

Website: www.idoj.in

DOI:10.4103/idoj.idoj_452_21

Quick Response Code:

pseudo-lymphoma, various patterns have been reported, from lichenoid and erythema multiforme (EM) like to leucocytoclastic and eczematous. Role of histopathology in predicting systemic involvement and thus final outcome remains elusive. Available literature suggests a possible role of degree of keratinocyte necrosis in predicting severity of visceral involvement.[1,4-7] Considering the range of cutaneous manifestations possible in DRESS, it is imperative to differentiate it from the much milder maculopapular drug rash (MPDR). Comparative studies differentiating DRESS from MPDR are also histopathologically limited. In the present study, we aim to correlate the histopathology of patients with DRESS with their investigative profile and compare their histopathology with patients diagnosed as MPDR. Further, histopathology of patients with drug rash (both DRESS and MPDR) having systemic involvement will be compared with those without systemic involvement to identify specific predictors.

Materials and Methods

A retrospective analysis of cases of cADRs diagnosed from July 2014 to July 2020 at a single tertiary care institute was performed after obtaining approval from Institutional Ethics Committee. A RegiSCAR score of ≥4 corresponding to probable or definite cases was used to recruit patients as DRESS.[8] In addition to data needed to calculate the RegiSCAR score, the following clinical details were retrieved and recorded: Age, gender, latency between the onset of eruptions and cutaneous biopsy, implicated drug, morphology of cutaneous lesions (diffuse erythema, purpura, pustules, and facial edema), and extent of skin involvement. To assess the visceral involvement, complete blood count, absolute eosinophil count, liver function test, and kidney function test were evaluated. RegiSCAR guidelines were followed to assess liver and kidney involvement. Further patients with a probable or definite diagnosis of cADR on the basis of Naranjo criteria and presenting with exanthem attaining a RegiSCAR score of ≤3 were categorized as MPDR in order to compare their histopathology with DRESS. Patients of both subtypes of drug rash (DRESS and MPDR) were also categorized depending on systemic involvement in order to identify specific histopathological predictors.

Histopathological evaluation was performed on hematoxylin and eosin-stained archival slide sections for both DRESS and MPDR. Two investigators (RJ, NS with over 12-year experience in dermatopathology) blinded to the final diagnosis reevaluated the histopathology and any discrepancy was settled after discussion. Histopathology changes enlisted were

a. In epidermis: Spongiosis (mild: focal spongiosis and severe: full thickness spongiosis with or without spongiotic vesicles), pustulation, keratinocyte dyskeratosis (mild: 1–10 cells/40×, severe: >10 cells/40×), basal vacuolization (mild: focal, severe: diffuse), Lymphocyte exocytosis (>10 lymphocytes/40× in minimum three fields)
b. In dermis: Papillary dermal edema (mild: focal, severe: diffuse), infiltrate density (sparse, intermediate, or dense), composition (lymphocytes, atypical lymphocytes, neutrophils, and eosinophils), red blood cell extravasation without vasculitis, leucocytoclastic vasculitis (LCV), presence of deep dermal infiltrate.

Atypical lymphocytes were defined as larger lymphocytes with enlarged hyperchromatic nuclei. LCV was defined as infiltration of vessel wall, fibrinoid necrosis, leucocyte karyorrhexis, and red blood cells extravasation. Histopathology pattern was labeled as lichenoid, EM like, eczematous, vasculitis, or pustular. When interface vacuolization with marked pigment incontinence and band-like lymphocytic infiltrate was present, it was regarded as lichenoid. In the presence of epidermal dyskeratosis, papillary dermal edema, and interface vacuolization, it was labeled as EM like. While, when severe spongiosis was seen in association with lymphocyte exocytosis, it was identified as eczematous.

The data were collected and entered in MS excel 2013. Statistical analysis was performed using SPSS software version 22. Descriptive statistics were calculated for quantitative variables. Frequency along with percentage was calculated for qualitative and categorical variables. Comparison of histopathology characteristics with investigative profile of patients with DRESS was done using Chi-square test. MPDR and DRESS were also compared for histopathological characteristics using Chi-square test.

Results

Eighteen patients of DRESS fulfilled the inclusion criteria. Men and women had an equal representation (M:F ratio 1:1). Age of the patients ranged from 8 years to 75 years with a median age of 35.5 years. Most common drugs implicated were anticonvulsants (27.8%), followed by antibiotics (22.2%) and antitubercular (22.2%) drugs. The latency period between initiation of drug and development of rash varied from 8 days to 60 days. Commonest cutaneous phenotype was urticarial papular exanthem (55.6%), followed by morbilliform rash (27.8%) and erythroderma (11.1%). Facial edema was a common feature seen in 72.2% cases. Body surface area involved ranged from 40% to 90%. Blood eosinophilia was encountered in 55.6% patients and deranged liver function and renal function were seen in 55.6% and 27.8% cases, respectively [Table 1]. Characteristic findings seen on histopathology were epidermal spongiosis (94.5%), epidermal dyskeratosis (33.3%), lymphocytic exocytosis (88.9%), interface vacuolization (77.8%), papillary dermal edema (100%), and perivascular lymphocytic infiltrate (100%) [Figure 1a and c]. Interface vacuolization was focal in 44.4% cases and diffuse in

Table 1: Clinical characteristics of the patients with drug rash with eosinophilia and systemic symptoms (DRESS) (*n*=18)

Clinical characteristics	Mean±SD/ number (%)
Age (years)	
Mean	39.00±20.65
Median	35.5
Gender	
Male	9 (50%)
Female	9 (50%)
Latency (days)	
Mean	17.7±12.6
Median BSA involved	60%
Offending drug	
Anticonvulsants	5 (27.8%)
Antitubercular	4 (22.2%)
Antibiotics	4 (22.2%)
Allopurinol	3 (16.7%)
Aceclofenac	1 (5.5%0
Ayurvedic	1 (5.5%)
Cutaneous phenotype	
Urticarial papular exanthem	10 (55.6%)
Morbilliform rash	5 (27.8%)
Erythroderma/exfoliative dermatitis	2 (11.1%)
EM-like lesions	1 (5.5%)
Facial edema	13 (72.2%)
Purpura	6 (33.3%)
Pustules	3 (16.7%)
Blood eosinophilia	10 (55.6%)
Liver dysfunction	10 (55.6%)
Renal dysfunction	5 (27.8%)

33.3% cases [Figure 2a and c]. Dermal infiltrate extended to involve deep dermis in half of the cases and in 94.5% cases, it comprised of eosinophils. In addition, 11.1% patients each had atypical lymphocytes, plasma cells, and neutrophils in the perivascular infiltrate. Red blood cells extravasation was observed in 55.5% cases; however, overt LCV was inconspicuous. In 13 of the 18 cases, histopathology could be classified into certain pattern. It was labeled as eczematous with lichenoid in three, EM like with lichenoid in two, lichenoid in three, eczematous in two, and pustular in one case. In two cases, a combination of eczematous, lichenoid, and EM-like pattern was seen [Figure 3a-d].

Comparison of histopathology changes with systemic involvement in terms of deranged liver or renal function did not reveal significant histopathological predictors except for association of papillary dermal edema with renal involvement [Table 2]. Histopathology characteristics of DRESS were compared with 20 cases of MPDR recruited on the basis of previously described

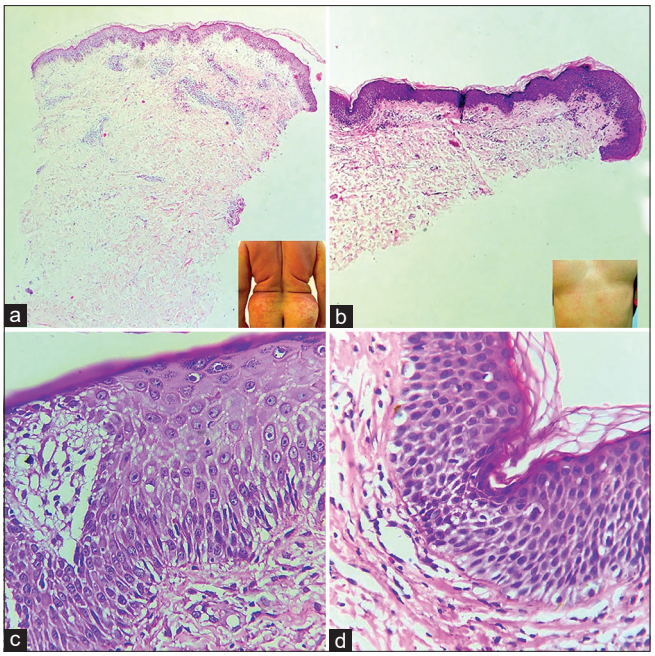

Figure 1: (a) Superficial and deep perivascular infiltrate in DRESS (H and E 4×) with inset showing urticarial papular exanthem over back, (b) mild superficial infiltrate in MPDR (H and E 4×) with inset showing maculopapular exanthem over chest and abdomen, (c) severe spongiosis with spongiotic vesicle in DRESS (H and E 40×), (d) mild spongiosis in MPDR (H and E 40×)

inclusion criteria [Table 3]. Statistically significant findings in favor of DRESS were lymphocytic exocytosis ($P < 0.001$), interface vacuolization ($P = 0.002$), severe spongiosis ($P = 0.046$), severe papillary dermal edema ($P = 0.018$), and higher density of dermal infiltrate ($P = 0.005$) [Figures 1a-d, 2a-d]. However, degree of epidermal dyskeratosis, tissue eosinophilia, and red blood cell extravasation was comparable in both ($P > 0.05$). In order to identify histopathological predictors of systemic involvement in patients presenting with drug reactions, patients of both subtypes of drug rash (DRESS and MPDR) were categorized on the basis of systemic involvement in terms of deranged liver and renal function as well as presence of blood eosinophilia. Lymphocyte exocytosis and distribution and density of dermal inflammatory infiltrate correlated significantly with deranged kidney function [Table 4]. Specific histopathological predictors could not be identified for liver involvement and blood eosinophilia.

Discussion

The mean age of patients with DRESS (39 ± 20.65 years) in the present study appeared younger when compared with reported literature.[1,7] The mean latency period between ingestion of culprit drug and onset of rash was 17.7 ± 12.6 days, corroborating with similar studies done worldwide.[1,7] Anticonvulsants and antimicrobials are the common culprit drugs; however, in addition, antitubercular drugs (22.2%) were also imputed in the reported study in a significant proportion of patients.

Table 2: Comparison of histopathology changes with systemic involvement in patients with drug rash with eosinophilia and systemic symptoms (*n*=18)

Histopathology characteristics	Liver function		Renal function		Blood eosinophilia	
	Deranged (*n*=10)	Normal (*n*=8)	Deranged (*n*=5)	Normal (*n*=13)	Present (*n*=10)	Absent (*n*=8)
Keratinocyte dyskeratosis						
Nil	6	6	2	10	5	7
1-10 cells/40×	4	1	2	3	4	1
>10 cells/40×	0	1	1	0	1	0
P	0.27		0.16		0.23	
Epidermal spongiosis						
Nil	0	1	0	1	1	0
Mild	6	3	2	7	4	5
Severe	4	4	3	5	5	3
P	0.41		0.64		0.49	
Interface vacuolization						
Nil	3	1	0	4	2	2
Mild	5	3	3	5	3	5
Severe	2	4	2	4	5	1
P	0.37		0.37		0.23	
Papillary dermal edema						
Mild	8	6	2	12	7	7
Severe	2	2	3	1	3	1
P	0.80		0.01		0.37	
Tissue eosinophilia						
Nil	0	1	0	1	1	0
Mild	8	6	5	9	7	7
Severe	2	1	0	3	2	1
P	0.49		0.37		0.57	

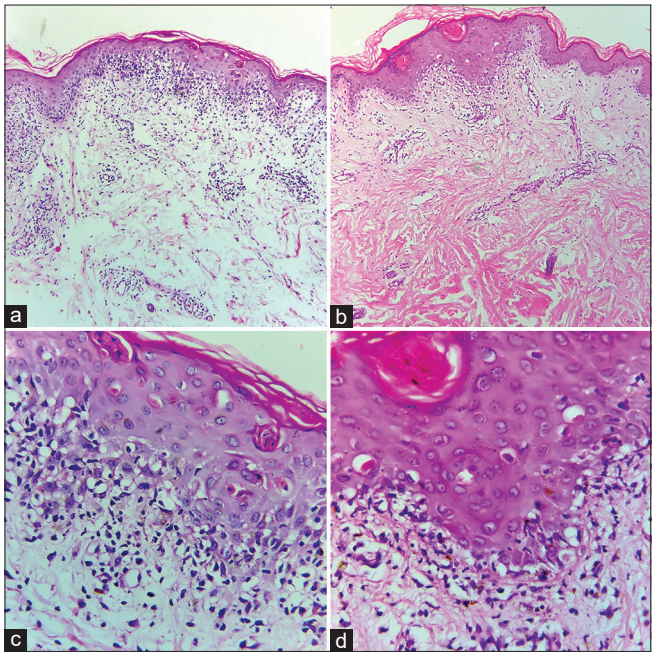

Figure 2: (a) Epidermal dyskeratosis with diffuse interface vacuolization in DRESS, H and E 10×, (c) H and E 40×. (b) Epidermal dyskeratosis with focal interface vacuolization in MPDR, H and E 10×, (d) H and E 40×

This possibly reflects the high prevalence of tuberculosis in our region. DRESS is characterized by a variable clinical as well as histopathological phenotype that lacks uniformity in reported studies. Walsh *et al.*[1] classified the clinical presentation of DRESS into urticarial papular exanthem, morbilliform eruptions, erythroderma, and EM like. However, there appears significant overlap with possible difficulty in definite categorization. Taking into account the predominant phenotype, most patients had urticarial papular exanthem (55.6%), followed by morbilliform rash (27.8%) and erythroderma (11.1%). Facial edema extending till neck has been especially associated with DRESS and a good proportion of patients present with purpuric and pustular lesions in addition to the predominant phenotype. Blood eosinophilia, atypical lymphocytes in peripheral blood, deranged liver and renal functions, lymphadenopathy, and pericarditis are important diagnostic hallmarks of DRESS having a place in the RegiSCAR score; however, none appears exclusive.[8] Blood eosinophilia was reported in 55.6% of our cases. Ortonne *et al.*[7] and Skowron *et al.*[6] reported higher proportion of patients with blood eosinophilia ranging from 89% to 97%. Variable representation of

Table 3: Comparison of histopathology characteristics of drug rash with eosinophilia and systemic symptoms (DRESS) and maculopapular drug rash (MPDR)

Histopathology characteristics	DRESS (*n*=18) Number (%)	MPDR (*n*=20) Number (%)	*P*
Epidermal spongiosis			0.046
Nil	1 (5.5)	1 (5.0)	
Mild	9 (50.0)	17 (85.0)	
Severe	8 (44.4)	2 (10.0)	
Epidermal dyskeratosis			0.844
Nil	12 (66.7)	15 (75.0)	
1-10 cells/400×	5 (27.8)	4 (20.0)	
>10 cells/400×	1 (5.5)	1 (5.0)	
Lymphocyte exocytosis	16 (88.9)	6 (30.0)	<0.001
Interface vacuolization			0.002
Nil	4 (22.2)	16 (80.0)	
Focal	8 (44.4)	3 (15.0)	
Diffuse	6 33.3)	1 (5.0)	
Papillary dermal edema			0.018
Nil	0 (0.0)	4 (20.0)	
Mild	14 (77.8)	16 (80.0)	
Severe	4 (22.2)	0 (0.0)	
Eosinophilia			0.488
Nil	1 (5.5)	0 (0.0)	
1-10/400×	14 (77.8)	15 (75.0)	
>10/400×	3 (16.7)	5 (25.0)	
RBC extravasation	10 (55.5)	12 (60.0)	0.782
Dermal infiltrate distribution			0.111
Superficial	9 (50.0)	15 (75.0)	
Superficial and deep	9 (50.0)	5 (25.0)	
Density of dermal infiltrate			0.005
Sparse	3 (16.7)	11 (55.0)	
Intermediate	9 (50.0)	9 (45.0)	
Dense	6 (33.3)	0 (0.0)	

systemic involvement between studies also reflects the level of care available at different institutes. In the study by Walsh *et al.*,[1] all cases had liver involvement and was attributed to theirs being a tertiary referral center for hepatobiliary diseases.

Histopathology of DRESS has not been well specified and is labeled as EM-like, spongiotic, lichenoid, or toxic epidermal necrolysis like, which in turn reflects the variable clinical phenotype.[7] Whether a particular histopathological pattern or character predicts systemic involvement and thus disease severity is also debatable. Presence of apoptotic or dyskeratotic keratinocytes has achieved significant attention with most studies correlating it with liver and renal dysfunction.[5,7] Drug-induced liver injury involves acute hepatocellular necrosis mirroring keratinocyte apoptosis. This is mediated by activated T-cells resulting in perforin granzyme B and Fas/Fas ligand-dependent cell death in both liver and skin.[9-11] In the present study, however, such association could not be established ($P > 0.05$). Further, none of the histopathological features correlated with systemic involvement except for papillary dermal edema, which was associated with renal involvement ($P = 0.01$).

Since DRESS can have variable clinical presentation and at times, differentiation from the benign MPDR can be challenging. Histopathology can help differentiate the two up to some extent with resultant better management. Significant findings favoring DRESS included severe spongiosis, lymphocyte exocytosis, interface vacuolization, papillary dermal edema, and moderate to severe density of perivascular dermal infiltrate. Ortonne *et al.*[7] also reported higher proportion of DRESS patients with interface dermatitis, dense dermal infiltrate, and atypical lymphocytes [Table 5]. In the present study though more cases with DRESS exhibited apoptotic keratinocytes; however, it failed to attain statistical significance. Chi *et al.*[5] reported dyskeratosis, spongiosis, and basal vacuolar damage as important features differentiating DRESS from MPDR. They further reported the most common

Table 4: Comparison of histopathology changes with systemic involvement in all patients (Both DRESS and MPDR, *n*=38)

Histopathology characteristic	Liver function		Renal function		Blood eosinophilia	
	Deranged (*n*=12)	Normal (*n*=26)	Deranged (*n*=11)	Normal (*n*=27)	Present (*n*=16)	Absent (*n*=22)
Epidermal spongiosis						
Nil	0	2	0	2	2	0
Mild	8	18	7	19	8	18
Severe	4	6	4	6	6	4
P	0.74		0.69		0.14	
Keratinocyte dyskeratosis						
Nil	6	21	7	20	9	18
1-10 cells/40×	4	5	4	5	6	3
>10 cells/40×	2	0	0	2	1	1
P	0.47		0.37		0.21	
Lymphocyte exocytosis	12	10	10	12	8	14
P	0.07		0.01		0.35	
Interface vacuolization						
Nil	4	16	4	16	7	13
Mild	5	6	5	6	4	7
Severe	3	4	2	5	5	2
P	0.27		0.32		0.22	
Papillary dermal edema						
Nil	2	2	0	4	2	2
Mild	7	23	9	21	11	19
Severe	3	1	2	2	3	1
P	0.08		0.29		0.33	
Tissue eosinophilia						
Nil	0	1	0	1	1	0
Mild	11	18	9	20	11	18
Severe	1	7	2	6	4	4
P	0.31		0.77		0.41	
RBC extravasation	8	14	5	17	814	
P	0.35		0.26		0.3	
Dermal infiltrate distribution						
Superficial	7	17	4	20	9	15
Superficial and deep	5	9	7	7	7	7
P	0.47		0.03		0.34	
Density of dermal infiltrate						
Sparse	4	10	1	13	5	9
Intermediate	7	11	5	13	7	11
Dense	1	5	5	1	4	2
P	0.57		0.003		0.41	

histopathological pattern in MPDR to be lichenoid (71%) followed by EM like (18%) and nonspecific (12%). Ortonne *et al.*[7] suggested identification of multiple patterns in one biopsy as a strong predictor of DRESS. We support their findings, with two-third of our cases having multiple histopathology patterns. Most common combination seen was eczematous with lichenoid in our series. Such combined patterns were inconspicuous in MPDR.

Many patients of MPDR also manifest systemic involvement ranging from deranged liver and renal function to blood eosinophilia; however, as they fail to achieve a RegiSCAR score of four or above, they are not classified as DRESS. Similarly, some patients of DRESS do not manifest systemic derangements. As there is therapeutic significance of systemic involvement, it is worthwhile to identify whether specific histopathological characters can predict it. In the reported study, lymphocyte exocytosis, presence of both superficial as well as deep dermal inflammatory infiltrate that is moderate to severe in density correlated significantly with deranged kidney function. However,

Table 5: Comparison of histopathology of DRESS among reported studies

Histopathology characteristics (%)	Present study (*n*=18)	Ortonne *et al*.[7] (*n*=50)	Walsh *et al*.[1] (*n*=27)	Skowron *et al*.[6] (*n*=45)	Sasidharanpillai *et al*.[4] (*n*=9)	Chi *et al*.[5] (*n*=32)
Epidermal spongiosis	99.4	-	59.2	55	55.5	78
Epidermal dyskeratosis	33.3	60	33.3	42	22.2	97
Lymphocyte exocytosis	88.9	64	-	-	44.4	91
Interface vacuolization	77.8	76	33.3	33	55.5	91
Papillary dermal edema	100	48	-	-	44.4	66
Eosinophilia	95.4%	20	-	84	33.3	72
RBC extravasation	55.5	-	88.8	46	-	53
Superficial and deep dermal infiltrate	50.0	26	-	41	33.3	-
Atypical lymphocytes	11.1	28	-	36	22.2	-
Density of dermal infiltrate (moderate to severe)	83.3	58	-	-	-	-

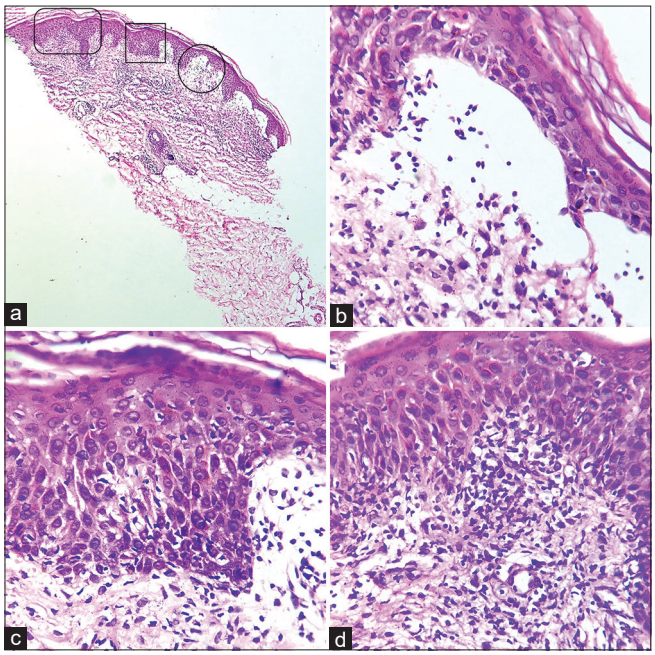

Figure 3: (a) Erythema multiforme like (circle), eczematous (square), and lichenoid (rectangle) pattern in a single biopsy of DRESS (H and E 4×), (b) keratinocyte dyskeratosis with papillary dermal edema and basal vacuolar damage representing erythema multiforme like pattern, (c) spongiosis with lymphocytic exocytosis representing eczematous pattern, (d) lymphocytic infiltrate at dermo-epidermal junction representing lichenoid pattern (H and E 40×)

such association could not be established with deranged liver function.

Thus, histopathology revealing prominent basal vacuolization, spongiosis, and dense dermal infiltrate is suggestive of DRESS. Presence of multiple histopathological patterns in a single biopsy should also be helpful in differentiating DRESS and MPDR. Presence of lymphocyte exocytosis (>10 lymphocytes/40X in minimum three fields), superficial and deep dermal infiltrate that is moderate to severe in density helps predict renal involvement in patients presenting with drug rash. The main limitations of the study are limited sample size and absence of objective assessment of histopathology characters including spongiosis, lymphocyte exocytosis, dermal edema, dermal infiltration, and basal vacuolization.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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