SPECTRUM OF MORPHOLOGICAL CHANGES IN ERYTHEMA MULTIFORME

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ABSTRACT

Objective: To evaluate the spectrum of morphological changes seen on histological examination of Erythema multiforme in a local population.

Material and methods: This descriptive study was conducted at Pathology Department of Pakistan Institute of Medical Sciences, Islamabad from January 2015 to January 2018. Out of 44 cases diagnosed with Erythema multiforme, 34 cases were included in the study according to inclusion/exclusion criteria. The cases having history of history of Stevens-Johnson syndrome and toxic epidermal necrolysis were excluded from the study. The microscpic features including epidermal changes and dermal changes were studied and recorded. All data was entered into SPSS version 24. Frequencies of various histopathological changes were calculated.

Results: The common histological feature shown in all 34 cases (100%) was perivascular inflammation, while the least common features were scab formation and ulceration (17.6% each). 2nd highest histological feature was hyperkeratosis and granulation tissue each (94.1%). There were 12 (35%) males and 22 (65%) females. The range of age in the present study was between 11 and 70 years. Eight (23.5%) patients were in the age group of 11 to 19 years and 22 (64.7%) were in the age range group of 40 to 70 years.

Conclusion: Microscopic features are varied but distinct which help in arriving at an accurate diagnosis of Erythema Multiforme. The most common histological feature is perivascular inflammation with interface inflammatory infiltrate. Other features include hyperkeratosis, granulation tissue formation, mucinous degeneration and acanthosis.

Key words: Erythema Multiforme, diagnosis, differential, keratinocytes, keratosis, blister, granulation tissue, inflammation.

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INTRODUCTION

Erythema multiforme (EM) is an uncommon condition involving the skin, mucous membranes or sometimes both[1]. The epidemiologic data available for Erythema multiforme is very much limited. The reason being the acute nature of the disease. In addition there is no recognized classification system. According to Samim et al. prevalence of erythema multiforme is less than 1%[2]. It is a self-limiting, acute, immune-mediated disorder. It is associated with hypersensitivity reactions to viruses and drugs.

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Among the viral infections, the herpes simplex virus is of primary type. In Erythema multiforme, there is the appearance of typical target-like lesions on the skin[3]. These lesions are less than 3 cm in greatest dimension and are characterized by at least three zones of somewhat different colours. These typical target lesions are considered as the hallmark for Erythema multiforme diagnosis. Erythema multiforme can also present with atypical targets lesions. The atypical lesions present as raised lesions usually have only two zones of colour change[4,5]. Whenever there is bullae formation in the centre of either the typical or atypical lesions of Erythema multiforme, it is a marker of epidermal involvement[6]. If the rash involves only skin, it is termed as Erythema multiforme minor, and if mucosal membranes are affected, it is called Erythema multiforme major[7,8]. Erythema multiforme was considered as a spectrum which includes Erythema multiforme minor, Erythema multiforme major, Stevens-Johnson syndrome(SIS) and toxic epidermal necrolysis(TEN)[9]. But later Bastuji-Barin et al. presented another grouping and describe Erythema multiforme

as a separate entity from TEN/SJS with distinct etiology, pathogenesis and clinical features[10]. Many causes of Erythema multiforme have been identified; out of which infectious etiology is most common[2], including Herpes Simplex Virus (HSV), Herpes Labialis, Mycoplasma pneumonia and Fungal infections[7,11,12]. Other cause include drugs like Sertraline[13], alendronate sodium[1], Infliximab[14], Herbal drugs[15], Barbiturates, NSAIDs, and Penicillins[3,16,17]. There are numerous disorders that may clinically present with skin or mucosal lesions that resemble with the manifestations of Erythema multiforme. That is why there is a long list of differential diagnosis which needs to be excluded from the erythema multiforme e.g. pemphigus vulgaris, paraneoplastic pemphigus, mucosal bullous pemphigoid, and linear IgA dermatosis. In addition, primary herpetic infection, other viral diseases such as hand-foot-mouth disease, erosive lichen planus, fixed drug eruption, lupus erythematosus, urticaria, cutaneous vasculitis, and some neutrophilic dermatoses have to be considered in the differential diagnosis of Erythema multiforme[3,8,18].

For diagnostic confirmation of Erythema multiforme and to differentiate it from other related disorders, clinical information is certainly the most important tool. However, other essential tools include histopathology, immunofluorescence and serological studies[7,19]. Immunofluorescence and electron microscopy are expensive diagnostic modalities. Pakistan is a developing country, where it is not possible to have immunofluorescence and electron microscopy in each and every laboratory center of Pakistan, therefore the reliance of diagnosing Erythema multiforme stays much on clinical correlation and accurate identification of histopathological features. Erythema multiforme presents with a wide spectrum of histological changes. A practicing histopathologist must be aware of theses varied histological features. In view of this rationale, the current study will focus on spectrum and frequency of these histological changes.

MATERIAL AND METHODS

This retrospective descriptive study was conducted at Pathology Department, Pakistan Institute of Medical Sciences, Islamabad from January 2015 to January 2018. A total of 34 out of 44 cases of Erythema multiforme fulfilled the inclusion/exclusion criteria. Skin biopsies of all age groups and both sexes were included in the study. The cases with autolysed tissue and cases having a history of Stevens-Johnson syndrome and toxic epidermal necrolysis were excluded from the study. The Non-probability purposive sampling technique was used. The blocks and slides of these cases were retrived from the hospital record. All the relevant information regarding the age, gender and date of procedure were retrieved from the hospital record management system and noted in the patient proforma sheet. The gross descriptive details i.e. measurements, weight and color were noted from the available biopsy reports. The slides were prepared from the tissue block in cases having the tissue blocks only or the cases in which the slides were broken or were of bad quality. The prepared slides were stained with Hematoxylin and Eosin (H&E). The criteria for microscopic morphology included epidermal and dermal changes. The epidermal changes studied during the research were hyperkeratosis, epidermal necrosis, scab formation, acanthosis, hemorrhage and ulceration. The dermal changes were categorized as perivascular inflammation, granulation tissue, mucinous degeneration of collagen and fibrin thrombi. All the microscopic findings were registered in the proforma. Cases were reviewed by two histopathologists, and the final diagnosis was rendered after consensus. All data was entered into SPSS version 24. Frequencies of various histopathological changes were calculated.

RESULTS

The most common histological feature shown in all 34 cases (100%) was perivascular inflammation, while the least common features were scab formation and ulceration (17.6% each) (Table 1). There were 12 (35%) males and 22 (65%) females. The most common age group was between 40 to 70 years with a total of 22 patients in the said group (65%) (Figure 1). Photomicrographs showed features of perivascular inflammation, acanthosis, hyperkeratosis and granulation tissue (figure 2 and 3).

Table 1: Frequency of different morphological features in the patients of Erythema Multiforme.

Morphological features	Present	Percentage
Perivascular inflammation	34	%100.0
Hyperkeratosis	32	%94.1
Granulation tissue	32	%94.1
Mucinous degeneration	27	%79.4
Acanthosis	21	%61.8
Epidermal necrosis	16	%47.1
Fibrin thrombi	17	%50.0
Hemorrhage	11	%32.4
Scab formation	6	%17.6
Ulceration	6	%17.6

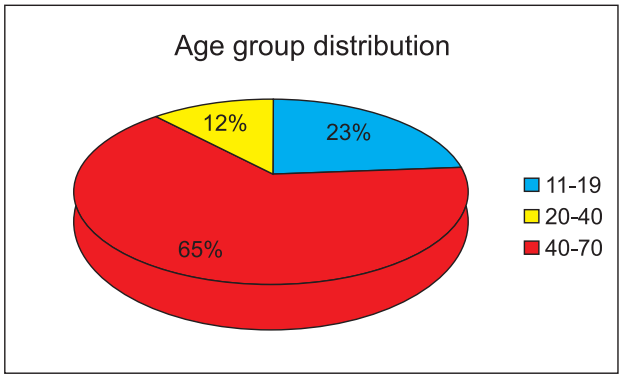

Fig 1: Age group distribution among patients of Erythema multiforme.

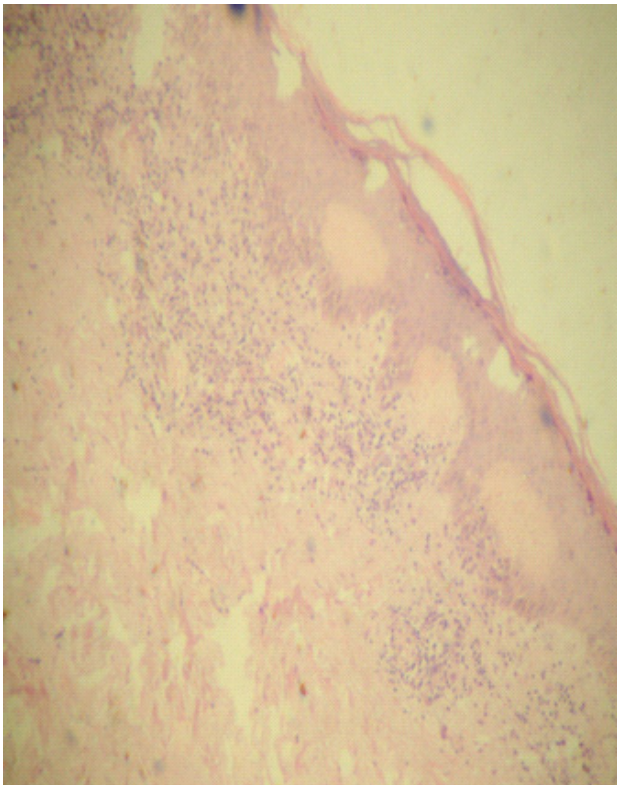

Fig 2: Photomicrograph of Erythema Multiforme, H & E, 10 x magnification.

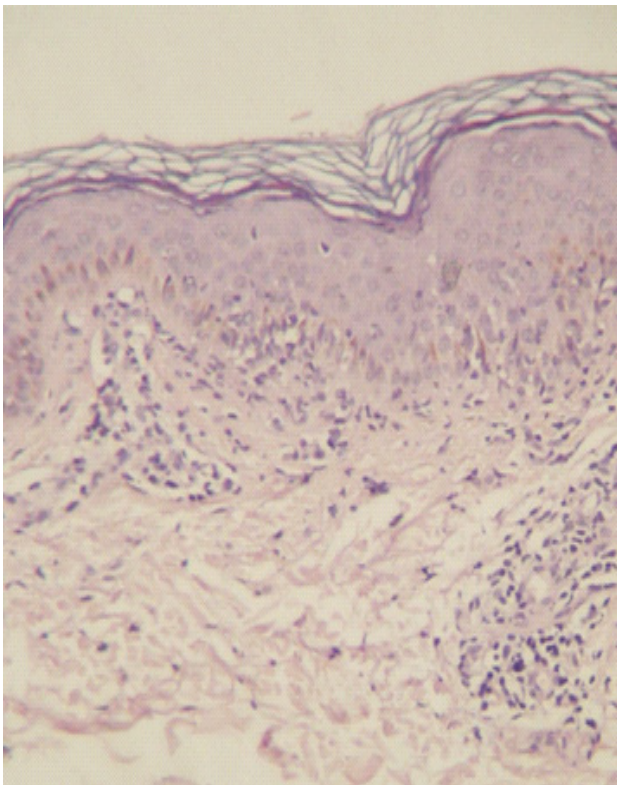

Fig 3: Photomicrograph of Erythema Multiforme, H & E, 20 x magnification.

DISCUSSION

Perivascular inflammation was the most prominent histological feature in all cases in our study. In addition to the perivascular inflammation, the interface dermatitis was also seen in 16 cases having epidermal necrosis as well. Most of the cutaneous inflammatory diseases present with perivascular dermatitis, however, the interface dermatitis narrows down the wide range of differential diagnosis for cutaneous inflammatory diseases. In interface dermatitis, there is a lymphocytic inflammatory response at the dermoepidermal junction, which ultimately leads to the apoptosis of keratinocytes. The death of the keratinocytes give rise to vacuolizations in the basement membrane, eventually leading to the formation of clefts. The top most important differential diagnoses of perivascular dermatitis with interface dermatitis with basement membrane vacuolizations are erythema multiforme, drug rash, pityriasis lichenoides[20,21].

In most of the cases, the inflammatory infiltrate comprised of lymphocytes and histiocytes. In addition to the lymphohistiocytic infiltration, nine cases were showing an appreciable number of neutrophils. There was predominance of eosinophils in 4 cases. In our opinion, the reason for the predominance of eosinophils in the 4 cases was due to drug hypersensitivity. However, it could not be confirmed as the history of the patients was not available. Presence of eosinophils in drug-related Erythema multiforme is also documented by other studies[22,23]. The Erythema multiforme caused by the Herpes virus usually do not show eosinophils[24]. Absence of eosinophils in most of the cases show that Erythema multiforme could be due HSV and not due to drugs. According to some authors, they have divided the histological features of Erythema multiforme into predominantly inflammatory pattern and predominantly necrotic pattern. It is seen in one of the studies that the nature of HSV induced Erythema multiforme was predominantly inflammatory, while the drug-induced Erythema multiforme was having predominantly necrotic pattern[25].

The second most common histological features were the hyperkeratosis and granulation tissue. Both of these features were present in 32 (94%) cases. The hyperkeratosis was in the form of orthokeratosis. As a part and parcel of immune-mediated situations, the immune cells play a vital role in the formation of granulation tissue. Mostly the macrophages and neutrophils are involved in granulation tissue formation[26].

The mucinous degeneration was seen in 27 (79 %) cases. In case of Erythema multiforme the blister formation shows hydropic degeneration and infiltration of mononuclear cells, especially the lymphocytes in the epidermis. There are also degenerative changes in the basal cell and keratin layer[21,27]. Acanthosis was present in 21 cases (62%) in our study. Buchner et al in his famous study,

found acanthosis in 76% out of total 25 cases[28]. The epidermal necrosis was seen in 16 cases (47%) (see table 1). A pattern of full-thickness epidermal necrosis was seen in 4 out of 16 cases having the epidermal necrosis. While the remaining 12 cases showed the epidermal necrosis which was limited to the lower 1/3rd layer of epidermis including the basal layer with interface dermatitis. The magnitude of having the epidermal necrosis may correlate with the age of the lesion. However, one point was noted that the lesion having limited epidermal necrosis showed stratum corneum with an intact basket woven appearance. These changes in the epidermis were also observed by bedi et al[29].

Papillary edema and hemorrhage were seen in 11 (32%) cases, which is ccontrary to a study done by Bedi et al in which it was present in all the cases[30]. This could be attributed to damage of the dermal blood vessels by the inflammatory infiltrate. The blood vessels are damaged by the inflammatory cells. They become leaky and show extravasation of red blood cells and plasma fluid to leak out leading to edema. It was observed that those cases in which there was papillary edema the severity of the epidermal necrosis was more. The logical reason for this increased amount of necrosis is that the epidermis does not have its own blood supply and it gets its nutrition and oxygen from the blood vessels in the dermis. So edema creates a barrier between the dermal blood vessels and the epidermis, which ultimately hampers the process of diffusion[7,28].

The fibrin thrombi were seen in 15 (44%) cases, which was also noticed by other studies.6 Scab formation was present only in 6 (18 %) cases and it was consistent with Lozada et al[30]. Ulceration was observed in 6 (18 %) cases. The ulceration is a common feature of the Erythema multiforme minor and is usually found in the oral mucosa. The lesion has an erythematous plaque-like appearance. Sometimes the lesions have active epithelial necrosis and may progress to superficial ulcerations. These ulcerations may have erosions with irregular edges[6,31].

The range of age in the present study was between 11 and 70 years. The age range is in accordance with the study done by Howland WWet al according to which the range of patients was between 10 and 70 years[32]. Nearly the same results are also published by Cretu et al[33]. Of these cases, 22 (65%) patients were in the 20 to 39 years' group. According to Cretu et al. the peak incidence in their retrospective study was also seen in the same age group[33]. Erythema multiforme is usually seen in the 3rd and 4th decade of life, but it can be present in children and adolescents[1,4,6,34]. Regarding gender, 65% of our cases were male and 35% were females. It was in contrast with Weintraub et al where 66.7% were females and 33.3% were males[4]. However other studies either mentioned that there is no gender predilection[1], or there was male predominance as highlighted by Shabahang et al and Sanchis et al respectively[11,35].

LIMITATION OF STUDY

Our study did not include immunofluorescence, electron microscopy and extensive clinical data, because of logistics issue. We hope further studies should be focused to overcome these limitations.

CONCLUSION

Microscopic features are varied but distinct which help in arriving at an accurate diagnosis of Erythema Multiforme. The most common histological feature is perivascular inflammation with interface inflammatory infiltrate. Other features include hyperkeratosis, granulation tissue formation, mucinous degeneration and acanthosis.

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under

Khan P:	Main idea, Practical work (Sample collection, preparation & microscopy)
Mudassar M:	Literature review, Discussion
Baloch FA:	Statistical analysis, Literature search, Conclusion
Waqas M:	Critical review of manuscript
Khan A:	Bibliography

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.