

**CLINICO-EPIDEMIOLOGICAL STUDY OF ERYTHEMA MULTIFORME**

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**ABSTRACT****BACKGROUND**

Erythema multiforme is an acute self-limited syndrome with distinctive skin lesions, with or without mucosal lesions, which can be precipitated by various agents. EM minor denotes mild cutaneous syndrome. EM major denotes more severe syndrome, with marked mucosal involvement.

**METHODS**

50 clinically diagnosed cases of erythema multiforme attending DVL department, attached to GGH Kurnool, were studied. A detailed proforma was taken, which included 1). Detailed history including chief complaints related to skin. 2). Complete physical and systemic examination. 3). Relevant investigations were done.

**RESULTS**

In the present study, 50 clinically diagnosed cases of erythema multiforme were enrolled. 31-50 yrs. (40%) age group patients showed peak incidence, with slight female preponderance. Incidence of EM minor (84%) was much higher than EM major (16%). Systemic drugs are the main cause for EM minor (50%) and the sole cause for EM major. Among drugs, Sulphonamides (20%) are the commonest cause. Next come Infections (30%) among which Herpes simplex (20%) is most common; followed by Radiotherapy. All cases of EM major showed symmetrical involvement, bullous lesions, erosions over both skin and mucous membranes. EM minor presented with papular lesions, 'Target' lesions over extremities.

**CONCLUSIONS**

The present study emphasises that EM can be diagnosed clinically. Drugs are the sole cause for EM Major.

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**BACKGROUND**

Erythema Multiforme is an acute self-limited syndrome with distinctive skin lesions, with or without mucosal lesions, which can be precipitated by various agents. EM minor denotes mild cutaneous syndrome. EM major denotes more severe syndrome, with marked mucosal involvement.

**METHODS**

The present study is conducted on 50 clinically diagnosed cases of EMF in the outpatient department of DVL, Kurnool Medical College, Kurnool from January 2011 to January 2012 for a period of 1 year.

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A detailed history regarding the age, sex, occupation, socio-economic status, duration of the disease, present and past illness, family and personal history was taken. A detailed dermatological examination is done noting the morphology and distribution of the lesions. The clinical diagnosis and classification are based on clinical appearance and involvement of mucous membranes. General physical examination and systemic examination done. Routine investigations like blood (total and differential count, ESR) urine examination are done. Blood sugar, urea, x-ray chest, ECG, culture of throat swab, fluid from bullae are done in relevant cases. Biopsy or skin lesions is done in few selected patients.

A detailed proforma was taken, which included:

1. Detailed history including chief complaints related to skin.
2. Complete physical and systemic examination.
3. Investigations were done in relevant patients.

**RESULTS**

In the present study 50 cases of clinically diagnosed cases of EMF are taken. In the present study age group of 31-50 yrs. shows the peak incidence.

Age	No. of Cases	%
0-10	4	8
11-20	4	8
21-30	8	16
31-40	10	20
41-50	10	20
51-60	9	18
Above 61	5	10
<b>Total</b>	<b>50</b>	<b>100</b>

**Table 1**

In this study incidence of EM is slightly high in females with ratio of male: female 1:1.3

In this study highest incidence of EM among house wives followed by labourers.

Occupation	No.	%
Children	2	4
Farmers	3	6
Housewives	17	34
Students	7	14
Labourers	9	18
Teachers	2	4
Executives	3	6
Sedentary Workers	3	6
Others	4	8

**Table 2**

In the present study the systemic drugs are the commonest cause of EM minor and sole cause of EM major. No significant seasonal variation noted. Incidence of EM minor (42 cases) is much higher than EM major (8 cases).

Type	No. of Cases	Percentage
EM Minor	42	84%
EM Major	8	16%

**Table 3**

In this study systemic drugs are the most common cause of EM minor(50%) and the sole cause of EM major, Sulphonamides (20%) being the commonest of known drugs, Infections (30%)especially Herpes simplex (20%) appears to be next common cause, followed by radiotherapy (5-10%)

In this study all cases of EM major showed bullous lesions and erosions over both skin and mucous membranes. All cases of EM minor showed Target lesions, few with papules. EM minor patients had burning sensation (50%) itching (24%) followed by pain (6%). In EM major all cases are associated with pain, burning, fever, myalgias etc. EM minor lesions are symmetrical, involving extensor aspects of extremities, palms & soles. In EM major cutaneous involvement was generalised, with mucous membrane involvement (oral, nasal, ocular, genital).

In this study drug induced EM appeared 1-3 days after the intake of the drug. In Herpes simplex induced cases EM appeared 7-14 days after the onset of lesions. In

Radiotherapy induced EM lesions occurred after 15-20 days of start of RT. In pregnancy EM developed in 2nd trimester.

In this study no evidence of systemic involvement was observed in EM minor and all cases of EM major showed systemic involvement.

	Aetiology	Em Minor	Em Major	Total
1.	Idiopathic	3	0	3
2.	Drug induced			
	Analgin	4	1	5
	Sulphonamides	5	5	10
	ATT	0	1	1
	Ibuprofen	1	0	1
	Unknown	7	1	8
3.	Infections			
	Herpes simplex lab	10	0	10
	Viral UTI	1	0	1
	Streptococcal	2	0	2
	Tuberculosis	1	0	1
	Bacterial dysentery	1	0	1
4.	Radiotherapy	5	0	5
5.	Pregnancy	2	0	2
	<b>Total</b>	<b>42</b>	<b>8</b>	<b>50</b>

**Table 4**

In the present study haemogram showed no significant abnormalities except for mild leukocytosis in 13 patients, raised ESR in 7 cases. Bacteriology showed mixed organisms.

Organism	Eye	Mouth	Skin	Urethra	Sputum	Stool	Blood
Staph aureus	6	4	3	1	-	-	-
Haemolytic Streptococci	-	1	-	-	1	-	-
E.coli	-	-	-	-	1	-	-
Gonococci	-	-	-	1	-	-	-

**Table 5**

Skin biopsy showed dermal oedema, resulting in dermal bullae, and perivascular mononuclear infiltrate. EM minor cases treated stopping the offending drug, Antihistamines, Topical steroid application, suitable antibiotic in cases associated with infection. All cases responded in 7-14 days. EM major cases treated by stopping the offending drug, systemic steroids Prednisolone 20-40 mg, suitable antibiotics, eye care, fluid and electrolyte balance, all skin lesions healed with hyperpigmentation without scarring in 20-25 days hyperpigmented lesions subsided over a period of 2-3 months.

**DISCUSSION**

**Incidence**

In the present study the annual incidence of EM is: 0.26%. The yearly incidence of EM at Johns Hopkins Hospital was 0.017% according to the study of Bianchine JR, Macaraeg PVJ, Lasagna L et al.<sup>1</sup> According to the Review of J. Clark Huff, William et al.<sup>2</sup> The annual incidence of "EM" was far less than 1%.

### Sex Incidence

In the present study there is slight female preponderance. Female to Male ration is 1.3:1. The study of W. Ashby, Therese et al<sup>3</sup> showed male preponderance. Female to Male ration Was 1:4.4 The study of S.S. Alubaidy and Fergal F Nally et al<sup>4</sup> showed female preponderance. Female to Male ration was 1.6:1. The study of Ting HC and Adam BA et al<sup>5</sup> showed male preponderance in EM major and female preponderance in EM minor.

### Age Incidence

In the present study the incidence of EM minor is higher in the age group of 31-50 years and that of EM major is below 30 years age group in both sexes. According to the study of W. Ashby, Theresa Lazar et al<sup>3</sup> the incidence of EM major was higher in below 30 years age group. According to the study of S. S. Alubaidy Fergal F. Nally<sup>4</sup> the incidence of EM was common in 18-49 years age groups. According to the review of J. Clark Huff, William L, et al<sup>2</sup> the incidence was higher in 20-40 years age group.

### Occupation

In the present study incidence is higher among house – wives and labourers which reflects the general incidence of patients attending the skin department, majority of whom are labourers.

### Seasonal Variation

In the present study no significant seasonal variation is seen. According to the study of Richard D. Sonthuna K. Richard et al<sup>6</sup> the incidence was higher during spring. According to the study of W. Ashby, Theresa Lazar et al<sup>3</sup> the incidence was higher during winter. According to the Review of J. Clark Huff, Wiluam L et al<sup>2</sup> there was no firm pattern to the occurrence.

### Clinical Types

In the present study the incidence of EM minor is higher than EM major, because in most of the cases aetiological factor was herpes simplex which usually produces EM minor and is a fairly common infection even among healthy people. According to the study of Ting HC and Adam et al<sup>5</sup> the incidence of EM major was higher than EM minor. According to the study of Ashby & Theresa et al<sup>3</sup> the incidence of EM major is higher than EM minor.

### Aetiology

In the present study systemic drug intake is found to be common cause (50%) in both types of EM, sulfonamide being the common drug. Herpes simplex is found to be the common cause EM minor. The higher incidence of drug induced EM in the present study can be attributed to the common practice of prescribing sulfonamides for routine infections because of its low price and also because of indiscriminate usage of analgesics. According to the study of Ting HC and Adam et al<sup>5</sup> EM major was frequently associated with drug intake. According to the study of Strom J et al Shelly WB et al Herpes simplex virus was the common cause

of EM. According to the study of Francia Lozada, Sol Silverman et al<sup>7</sup> the causative factors constitute 52% idiopathic, 20%, emotional stress, 16% food products, 14% Herpes, 4% drugs.

According to the study of Bianchin J. R. et al<sup>1</sup> Drug intake was the most frequent causative factor and among drugs penicillin was the commonest drug followed by short acting sulfonamides. According to the study of S. S. Al – Ubaidy and Fergel et al emotional stress (24%), Penicillin therapy (12%), Herpes simplex (6%) were the common causes. According to the study of Richard D Sontheimer et al<sup>9</sup> Drugs and infection were the common causes. Of EM.

### Type of Lesion

According to the study of S. S. Al - Ubaidy and Fergel et al<sup>4</sup> the commonest lesion was Target lesion. According to the study of Lynch F. W. et al<sup>8</sup> Target lesion was the commonest lesion. According to the study of W. Ashby et al<sup>3</sup> Target lesion and bullous lesions were commonest lesions. In the present study Target lesion is found in all cases of EM minor and erythematous macules and bullous lesions in EM major cases. The above discrepancy in the incidence could be explained by the fact that present study was conducted in GGH where infections are common presenting problems than drug related problems

### Associated Symptoms

In the present study EM minor is associated with burning sensation and itching. Constitutional symptoms during the prodrome and course of illness are observed only in EM major cases. According to the study of Ting HC & Adam BA et al<sup>5</sup> association with prodromal and constitutional symptoms was present in EM major only. According to the study of S. S. Al Ubaidy & Farget Nally et al<sup>4</sup> constitutional symptoms were present in EM major (45%). According to the study of W. Ashby, Theresa Lazar et al<sup>3</sup> prodromal symptoms were present in EM major cases (47%).

### Site of Involvement

In the present study extensor aspect of extremities and Palms and soles are the commonest sites involved in EM minor and generalized involvement in EM major. According to the study of Al Ubaidy and Fergal et al<sup>4</sup> dorsal surfaces of extremities were the common sites of involvement. According to the study of W. Ashby, Theresa et al<sup>3</sup> Palms and soles were often affected, scalp was free from involvement. Scalp is not affected. Mucous membrane involvement is rare and mild in EM minor, constant and severe in EM major.

### Duration of The Illness

In the present study the duration of illness varied from 7 – 14 days in EM minor and 20-30 days in EM major. According to the study of W. Ashby, Theresa Lazar the duration of illness varied from 5-46 days (3 weeks). According to the study of S. S. Al Ubaidy & Fergal F. Nally et al<sup>4</sup> the duration of illness was 15 days. According to the study of Francia Lozada et al the duration of illness was from 2 weeks to 6 months.

### Systemic Involvement

In the present study those cases which have not shown any evidence of systemic involvement are classified as EM minor. According to the study of Ting HC and Adam et al<sup>5</sup> in EM major systemic involvement was 47% and no systemic involvement in EM minor. According to the study of W. Ashby and Theresa Lazar et al<sup>3</sup> Pulmonary involvement was 37%. According to the study of Bianchin JR, Macareag PVJ, Lasagna L et al<sup>1</sup> Pulmonary involvement was 15-30%. Schartum et al reported two cases of EM major with cardiac involvement. Comaish JS et al reported a case with nephritis. Gastrointestinal and respiratory tract are at least to some extent involved in all cases of EM major (16%) Central nervous system, Cardiovascular system are not affected. Only 2 cases (4%) of EM major are associated with transient albuminuria (2 days).

### Associated Diseases

In the present study also, similar observation was noted. According to the review of J. Clark Huff, William L et al no particular disease either cutaneous or systemic was associated with EM.

### Investigations

In the present study also in accordance with other studies, laboratory tests are not Diagnostic Histopathology is non – specific. According to the study of W. Ashby, Theresa Lazar,<sup>7</sup> et al investigations were not diagnostic, except for raised ESR in a few severe cases. According to the study of S. S. Al – Ubaidy et al<sup>4</sup> investigations were not diagnostic and histopathology was non – specific. According to the study of Francina Lozada et al the investigations were within normal limits and histopathology was nonspecific with vascular involvement.

### Treatment and Response

In the present study there is good response to symptomatic treatment in EM minor cases and to the earlier introduction of systemic corticosteroids in EM major cases. According to the study of Rasmussen JE et al<sup>9</sup> treatment with systemic corticosteroids did not change the prognosis. According to the study of W. Ashby et al<sup>3</sup> symptomatic treatment and systemic steroids showed good response. According to the study of S. S. Al Ubaidy et al<sup>4</sup> treatment was mainly symptomatic. Prognosis was good with systemic steroids.

### Complications and Mortality

In the present study there is no permanent sequelae in EM minor and no permanent cutaneous sequelae in EM major. Two cases (4%) of EM major developed permanent visual impairment. Mortality is nil. According to the study of Nathan et al mortality was 3-25% and eye complications were seen in 3-10% of the cases. According to the study of Arstikaites et al ocular complications were seen in 3 -10 % of the cases. Stun MR, Thompson et al<sup>10</sup> reported a case with oesophageal stricture following SJ syndrome. Hersel JM, Gaylor et al reported a case of vesicle calcification following SJ syndrome. Comaish et al reported inflammatory renal

lesions similar to acute glomerulonephritis, subacute nephritis, nephritic syndrome and chronic uraemia. Mortality was 5 – 15%. J. Dalgard JB, Scott D<sup>11</sup> reported 4 cases of SJ syndrome complicated by ulcerative colitis and ulcerative proctitis. According to the study of W. Ashby mortality was 22%.

### Relapses

In the present study relapses are noted in ten cases (20%) of EM minor and in one case of EM major. Herpes simplex is commonly associated with relapses. According to the study of Nathan MD et al relapse rate was 13%. According to the study of Ashby DW et al<sup>3</sup> relapse rate was 23%.

### CONCLUSIONS

Among the patients attending the department of Dermatology, Medical College Hospital, Kurnool, from January 2011 to January 2012, fifty cases are diagnosed as erythema multiforme and are studied in detail. The findings are summarized as follows- The incidence of erythema multiforme is 0.26%. Females are affected relatively more frequently than males in a ratio of 1.3:1. The incidence of EM minor is higher in the age groups of 31-50 in both sexes (50%). The incidence of EM major is higher in below 30 years age group in both sexes (75%). The incidence of EM is higher among housewives (34%) and labourers (18%). No significant seasonal variation is noted. EM minor constituted 84% and EM major 16% of the EM cases. Systemic drug intake is found to be the causative factor in 50% of EM minor cases and 100% of EM major cases. Sulfonamides and Analgin are the commonest drugs involved in the causation of the disease. Herpes simplex is associated with 20% of EM minor cases. Target lesion is the commonest lesion in EM minor, Bullous lesion is the commonest lesion in EM major.

Prodromal symptoms are observed in EM major cases only. Burning sensation is the commonest symptom in both types of EM. In EM minor cutaneous involvement is more or less symmetrical. Extensor aspects of extremities, palms (Figure 1) and soles are the commonest sites of involvement. Scalp is not affected. Mucous membrane involvement is mild and rare. In EM major cutaneous involvement is generalized and is marked over the trunk. Mucous membrane involvement is severe and constant (Figure 3). In EM minor, duration of illness is 7-14 days. In EM major, duration of illness is 20-30 days. In EM minor cases, there is no evidence of systemic involvement. Gastrointestinal system and respiratory system are affected in all cases of EM major but cardiovascular, central nervous systems are not affected. Transient albuminuria is found in 2 cases of EM major. Herpes simplex labialis is the commonest diseases associated with EM minor. Routine laboratory tests performed in the evaluation of subjects with EM are not diagnostic. Histopathology is nonspecific. EM minor cases responded well to symptomatic treatment.

Earlier introduction of systemic corticosteroids in EM major cases showed good response. No permanent sequelae are found in EM minor cases. No permanent cutaneous

sequelae are found in EM major cases. Two cases of EM major developed permanent visual impairment. Relapses were seen in ten cases (20%) of EM minor and one case of EM major. Herpes simplex is commonly associated with relapses.



**Figure 1. EMF- Palms**



**Figure 2. Target Lesions**



**Figure 4. EMF Major**

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