

A Clinico-Etiological Study of Erythroderma in Adults in a Tertiary Care Centre

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ABSTRACT

BACKGROUND

Erythroderma is a clinical entity that may cause severe systemic manifestations. The difficulty with erythroderma lies in finding the underlying aetiology. It is imperative to demonstrate precise aetiology whenever possible so that distinct therapy may be initiated. At times, despite finding the aetiology, relapses constitute a great menace. The purpose of our study was to assess the clinical profile and aetiology of erythroderma. Besides, the study also illustrated factors leading to relapses; such studies are rare in literature.

METHODS

This hospital-based, cross-sectional study included 88 patients of erythroderma of either sex and age more than 18 years; their clinical, laboratory, histopathological findings, treatment and outcome were studied.

RESULTS

The mean age of onset was 47.3 ± 12.35 years with the male to female ratio being 2.38:1. The most common cause of erythroderma was pre-existing dermatoses (67 %) followed by drugs (10.2 %), infections (3.4 %), malignancies (4.54 %), and idiopathic (14.7 %). Psoriasis was the predominant aetiology (45.4 %) among the pre-existing dermatoses with a maximum number of relapses ($P = 0.02$). Psoriasis was significantly associated with pruritus ($P = 0.001$), subungual hyperkeratosis ($P = 0.0001$), palmoplantar keratoderma ($P = 0.001$). Clinico-histological association was found in 64.6 % of cases. Mortality was seen in 6.8 % of cases.

CONCLUSIONS

As in previous studies, pre-existing dermatoses were the most common causes in our study; albeit, a special emphasis on factors leading to relapses was given to prevent further episodes. The most common factor of relapse was uncontrolled comorbid disorders (diabetes and hypertension) followed by medication nonadherence. Hence, our study suggests a need for more effective comorbidity management and creating awareness regarding judicious use of drugs which can go far in preventing mortality and morbidity.

KEY WORDS

Erythroderma, Adults, Aetiology, Relapses, Comorbidities.

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BACKGROUND

Erythroderma is a generalized inflammatory disorder of the skin manifesting with erythema and scaling affecting more than 90 % of the skin surface.¹ It is one of the few dermatological conditions requiring hospitalization and multisystem management. Erythroderma is considered a complex system that may be the result of many different causes. The diagnosis of the underlying cause may be very difficult but it is important to find aetiology for the appropriate intervention of each case.

Objectives

To evaluate demographic profile, clinical features, aetiology of erythroderma and correspond the clinical diagnosis with histopathology.

METHODS

This cross-sectional study was conducted between January 2017 and June 2019 (30 months) at a tertiary care teaching hospital located in Southern India. 88 successive erythroderma patients aged above 18 years were included in the study. Pregnant and lactating women were excluded from the study. The study was recognized by the institute scientific and ethics committees and written informed consent was procured from all patients.

Study patients were enlisted from dermatology outpatient clinics and referrals from other departments and convenience sampling was followed. All patients were admitted and were evaluated with detailed history and complete physical examination. History included the onset and evolution of erythroderma, history of pre-existing dermatoses, previous episodes of erythroderma, aggravating factors, comorbidities and drug intake. A detailed clinical examination was done to know the various clinical manifestations and also find out the possible causes for the erythroderma.

History of silvery scaly plaques and heavier involvement in body parts where psoriasis was common helped in making out psoriatic erythroderma. Typical nail changes of psoriasis and psoriatic arthritis if present are clues to psoriasis. Strong history of contact allergy, presence of previous eczematous lesions and also severe oozing lesions will help to diagnose the allergic contact dermatitis as the cause of erythroderma, which was confirmed by patch testing. Ingestion of suspected drugs before the onset and acute onset with fever will help in the diagnosis.

Diagnosis of idiopathic erythroderma could be made when the condition is extending over 1 month in an elderly with severe pruritus with palmoplantar keratoderma. Cutaneous lymphoma presents with similar findings of idiopathic erythroderma, keen histopathological examination and follow-up biopsy will help to make out the diagnosis.

Laboratory investigations such as complete hemogram, blood glucose, renal function tests, liver function tests, serum electrolytes, erythrocyte sedimentation rate, serum protein levels, urine microscopy, serum markers for viral hepatitis B and C and HIV antibody testing were performed. Wherever

necessary, chest radiograph, ultrasound, peripheral blood smear, fine needle aspiration cytology of lymph nodes, patch testing, microscopy for scabies mite and fungus were done. Skin biopsy for histopathological examination was performed in 62 cases (70.45 %). We have also examined data concerning management, outcome, relapses and complications when available.

Statistical Analysis

The findings were recorded on a specially designed master chart and statistical tests were done using Epi info software version 7.2.2.6 and analyses were done at a 5 % level of significance and a P-value of < 0.05 was considered significant. Chi-square test was applied to obtain the P-value.

RESULTS

The mean age of onset was 47.3 ± 12.35 years with the age of the patients ranging from 21 to 78 years. The majority of the patients belonged to the age group of 40 - 49 years (38 cases) (43.1 %) and a minimum number of patients in 70 - 79 years group (4 cases) (4.54 %). There were 62 males (70.5 %) and 26 females (29.5 %) with a male to female ratio being 2.38:1, showing male preponderance.

The mean duration of onset of erythroderma was 46 days (median = 60 days) (range: 1 day–18 months). Progression of the disease was in less than 6 - 8 weeks in 72 patients (81.8 %); albeit, 12 patients showing sudden progression within 3 - 4 days were seen in psoriasis. A longer duration of more than one year was seen in cutaneous lymphoma and psoriasis. In the study, psoriasis was the entity with a varied duration of onset ranging from few days to more than one year.

In the study, comorbidities were recorded in 58 patients (65.9 %). The most common comorbidities documented were hypertension (42 patients), diabetes (33 patients), tuberculosis (three patients), HIV / AIDS (four patients) and epilepsy (four patients). 75 % of patients with psoriasis (30 patients out of 40) had at least one comorbidity in their past medical history.

Pre-existing dermatoses were recorded in 27 patients (30.6 %) which comprised psoriasis (22 patients), eczema (five patients).

Table 1 illustrates the characteristics of the patients and a summary of the results of the study.

Clinical Features and Laboratory Investigations

Besides generalized erythema and scaling, clinical features included pruritus (49 / 88 patients; 55.6 %), shivering (26 / 88 patients; 29.5 %), malaise (41 / 88 patients; 46.5 %), pedal oedema (43 / 88 patients; 48.8 %), fever (18 / 88 cases; 20.4 %), palmoplantar keratoderma (55 / 88 patients; 62.5 %), nail changes (64 / 88 patients; 72.7 %), lymphadenopathy (28 / 88 patients; 31.8 %). (Figure 1a,1b). Hypoalbuminemia (16 / 88 patients; 18.1 %) is attributed to loss of proteins in the form of scales and hepatic insufficiency.

Aetiology

In the study, patients were categorized into five etiologic groups as illustrated in Figure 2: (1) Pre-existent dermatoses (66.9 %) (2) infections (3.4 %) (3) drug reactions (10.2 %) (4) malignancy (4.5 %) (5) idiopathic or undetermined (14.7 %). Pre-existing dermatoses comprising psoriasis and eczemas contributed the highest percentage of erythroderma as seen in 59 patients (66.9 %). Psoriasis was the most common pre-existing dermatosis causing erythroderma (40 / 88 patients;

45.4 %) (Figure 1c). Erythroderma had arisen on pre-existing longstanding psoriasis in 22 patients with a mean period of 557 days and median period of 90 days (ranges: 4 days and 7 ½ years). Acute onset of erythroderma was seen in 12 patients and all of them had a history of psoriatic arthritis (P = 0.02). 14 psoriasis patients had relapses and among them, 10 patients had significantly longer duration of psoriasis (P = 0.002) [mean = 2.5 years and median = 1 1 / 2 year (range: 1–7years)].

Aetiology	Psoriasis 40 cases (45.4 %)	Eczema 19 cases (21.5 %)	Infections 3 cases (3.4 %)	Drug 9 cases (10.2 %)	Malignancy 4 cases (4.54 %)	Idiopathic 13 cases (14.7 %)
Age Mean(years)	41.35	53.75	46.3	46.5	49.75	57.6
Sex ratio	2	2.8	3 cases are males	2	4 cases are males	1.6
Pre-existing dermatoses	22	5	-	-	-	-
Clinical features						
Pruritus (49 cases)	30	6	3	3	2	5
Shivering (26 cases)	10	3	-	5	2	6
Malaise (41 cases)	16	6	1	7	3	8
Pedal oedema (43cases)	22	10	-	3	2	6
Fever (18 cases)	7	-	-	8	-	3
Oliguria (10 cases)	3	1	-	3	1	2
Nail changes (64 cases)	36	11	3	2	2	10
Palmoplantar keratoderma (55 cases)	36	9	1	4	-	5
Conjunctival congestion (23 cases)	10	2	-	6	2	3
Scalp involvement (31 cases)	25	1	-	-	1	4
Oral mucosa (14 cases)	5	-	-	6	1	2
Lymphadenopathy (28 cases)	13	2	1	2	4	6
Hepatosplenomegaly (4 cases)	-	-	-	1	1	2
Deck chair sign (4 cases)	2	1	-	-	1	-
Nose sign (6 cases)	3	2	-	-	-	1
Laboratory investigations						
Anaemia (16 cases)	6	1	-	3	2	4
Hypoalbuminemia (24 cases)	13	3	-	3	1	4
Eosinophilia (7 cases)	-	-	-	4	3	-
Atypical lymphocytes (2 cases)	-	-	-	-	2	-
Altered Liver function tests (16 cases)	5	2	-	4	1	4
Altered kidney function tests (14 cases)	4	2	-	3	-	5
Outcome	Lost to follow up - 6 Clearance - 32 No response - 2	Lost to follow up - 2 Clearance - 15 No response - 2	Clearance - 3	Lost to follow up - 0 Clearance - 8 Mortality - 1	Clearance - 1 No response - 2 Mortality - 2	Lost to follow up - 5 Clearance - 3 No response - 2 Mortality - 3

Table 1. Demographical, Clinical, Laboratory, Therapeutic and Evolutive Features of the 88 Patients with Erythroderma According to Aetiology (n = 88)

Clinical Diagnosis	Number of Biopsies	Histopathological Diagnosis
Psoriasis (40 cases)	26	Psoriasis - 24 Non-specific - 2
Eczema (19 cases)	12	Eczema - 8 Non-specific - 4
Infections (3 cases)	3	Dermatophytosis - 2 Scabies - 1
Drug (9 cases)	5	Drug reaction - 3 Non-specific - 2
Malignancy (4 cases)	4	Malignancy - 4
Idiopathic (13 cases)	15	Eczema - 3 Non-specific - 12

Table 2. Correlation between Histological and Clinical Diagnosis

Author(s), years	Number of Patients (N)	Pre - Existing Dermatoses (%)	Drug (%)	Malignancy (%)	Idiopathic (%)
Other countries					
Nicolis and Helwig et al. (1973)	135	27	40	8	12
Hasan and Jansen (1983)	50	54	10	4	32
King et al. (1986)	82	31	34	18	16
Wilson et al. (1993)	50	48	8	4	32
Pal and Haroon (1998)	90	74	5.5	5.5 %	14.6
Sehgal et al. (2004)	80	58	20	0	22
Akhvani et al. (2005)	97	59.8 %	21.6	11.3	7.2
Khaled et al. (2010)	82	43.9	21.95	4.87	25.6
In India					
Hulmani et al. (2014)	30	63	16.6	3.3	16.6
Banerjee S et al. (2015)	32	62.5	12.5	0	25
Present study	88	67	10.2	4.54	14.7

Table 3. Causes of Erythroderma in Previous Studies Compared with the Present Study



Figure 1. Clinical Features of Cases 1a) Palmar Keratoderma 1b) Subungual Hyperkeratosis 1c) Psoriatic Erythroderma 1d) Erythroderma Due to Stasis Eczema 1e) Histopathological Features of Biopsy (10 x)(H & E) Psoriasiform Dermatitis Showing Hyperkeratosis, Parakeratosis, Elongation of Rete Ridges

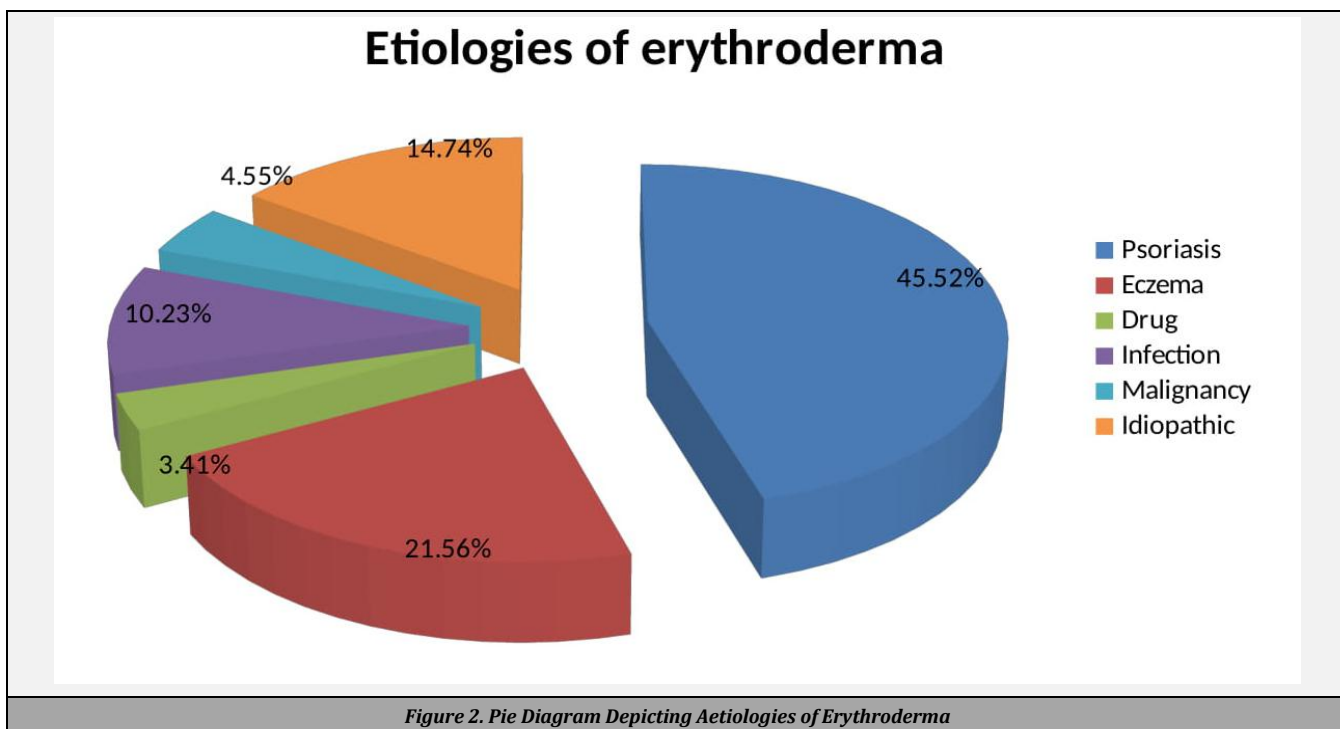


Figure 2. Pie Diagram Depicting Aetiologies of Erythroderma

Eczema was the cause of erythroderma in 21.5 % of patients (19 / 88 patients) (Figure 1d). Eczemas documented were: allergic contact dermatitis (ACD) (seven patients), airborne contact dermatitis (ABCD) (seven patients) and stasis eczema (five patients). ACD was due to paraphenylenediamine (two patients), *Semecarpus anacardium* / bhilawa seeds (one patient), cement (two patients), nickel (two patients). ACD was diagnosed by patch testing. ABCD due to parthenium weed was the cause of erythroderma in seven patients.

Infections implicated in causing erythroderma were extensive dermatophytosis (two patients), crusted scabies

(one patient). Factors responsible for the flare-up of dermatophytosis to erythroderma were erratic use of topical corticosteroids.

Drug-induced erythroderma was identified in nine patients (10.2 %). Incriminated drugs were phenytoin (three patients), Isoniazid (two patients), carbamazepine (one patient), nevirapine (one patient), dapsone (one patient), terbinafine (one patient). The patient with dapsone induced erythroderma was diagnosed as a case of lepromatous leprosy and was put on multidrug therapy (dapsone, rifampicin and clofazimine) one month prior to the development of

erythroderma.

In malignancy induced erythroderma, two patients had mycosis fungoides (MF), one of which was granulomatous slack skin variant; two patients suffering from Hodgkin's lymphoma (HL), mixed cellularity variant.

Despite detailed investigations and multiple serial skin biopsies, no cause could be identified in 13 patients. (14.7 %) (eight males, five females).

Some aetiologies were significantly associated with certain clinical signs.

1. Subungual hyperkeratosis (34 patients) and psoriasis (P = 0.0001).
2. Palmoplantar keratoderma (34 patients) and psoriasis (P = 0.0001)
3. Pruritus (30 patients) and psoriasis (P = 0.001)
4. Relapses (14 patients) and psoriasis (P = 0.02)
5. Longer duration of psoriasis (10 patients) and relapse (P = 0.002)

Clinicopathological Correlation

Skin biopsy was obtained in 62 patients. Three of them had two biopsies (a total of 65 biopsies). Histological examination inferred a specific dermatosis in 42 biopsies (42 / 65:64.6 %). The remaining 23 biopsies (35.3 %) were concluded to non-specific dermatitis (Table 2). Most common histopathological findings were perivascular lymphocytic infiltrate (24 / 65 biopsies; 36.9 %) followed by parakeratosis (20 / 65 biopsies; 30.7 %). The presence of parakeratosis, hypogranulosis, suprapapillary thinning, acanthosis and perivascular lymphocytic infiltrate were suggestive of psoriasis (Figure 1e). Hyperkeratosis, spongiosis, perivascular lymphocytic infiltrate and eosinophils were in favour of eczemas. The presence of parakeratosis, basal cell vacuolization, perivascular lymphocytic infiltrates and eosinophils was suggestive of drug-induced erythroderma.

Lymph Node Biopsy

In the study, nine lymph node biopsies were performed. Out of which, four biopsies revealed malignancy while five showed dermatopathic lymphadenopathy. Immunohistochemistry was done in four patients with malignancy induced erythroderma which revealed CD 30 positivity in HL and CD 3,4,7 positivity in MF. Lymphadenopathy regressed over a period of 1 - 2 weeks, as an erythrodermic state was treated in dermatopathic lymphadenopathy.

Treatment

Treatment included a combination of topical and systemic agents. Emollients, moisturizers, topical corticosteroids were a mainstay of topical therapy. Systemic agents administered were methotrexate (32 psoriasis patients), acitretin (8 psoriasis patients), cyclosporine (three psoriasis patients) dexamethasone (six drug reactions, five ABCD, four stasis eczema, five ACD, five idiopathic, one mycosis fungoides), chemotherapy (ABVD regimen for one HL patient), PUVA therapy (two psoriasis patients, two idiopathic patients, two MF patients). (Table 1)

Relapses

Relapse rate was 22.7 % (20 patients) after a mean remission of 5.2 months (median = 3 months) (range: 20 days -2 years) with:

One relapse: 13 patients (psoriasis: 8 patients, MF: 2 patients, idiopathic: 2 patients, ABCD: 1 patient)

Two relapses: 6 patients (psoriasis: 5 patients, ABCD: 1 patient)

Three or more relapses: 1 patient (pustular psoriasis: 1 patient)

Relapse both in terms of the number of patients (14 patients) and the number of episodes (3 episodes) was highest in psoriasis. The case with three relapses was a female patient with generalized pustular psoriasis.

The most common causes of relapse were uncontrolled comorbid disorders (diabetes and hypertension) seen in 12 patients (13.6 %) followed by medication non-adherence seen in five patients (5.7 %). Other causes being the winter season, parthenium weed and emotional stress

Mortality

Mortality in our study was observed in six patients (6.8 %): two patients of MF, one patient of nevirapine induced erythroderma in HIV / AIDS with a CD4 count of 22, three patients of idiopathic erythroderma, sudden cardiac death, acute respiratory distress syndrome were the causes of death.

DISCUSSION

Erythroderma is uncommon with an incidence of 1 - 2 / 100,000 population.² A prospective study done by Sehgal and Srivastava in India resolved the incidence to be 35 per 100,000 dermatologic patients,³ while another study by Hasan and Jansen also approximated the annual incidence to be 1 to 2 per 100,000 population.⁴ There is a male preponderance in most studies with a male-to-female ratio ranging from 2:1 to 4:1 and the mean age between 40 and 60 years.² This is similar to our study where the male-to-female ratio was 2.38:1 with a mean age of 47.3 years. The onset of erythroderma is usually gradual and insidious.^{5,6} As there is no available standard demarcation of chronic and acute onset erythroderma, we considered the cases with clinical features started in the preceding 2 weeks as acute onset erythroderma. In our study, psoriasis was the only entity that had both acute and chronic onset ranging from 4 days to 2 years. This is in contrast to previous studies where drug-induced erythroderma had acute onset.^{7,8}

Similar to other studies, majority of the clinical features did not correlate with aetiology. Despite varied causes, erythroderma has several common clinical features.^{2,6,9} In our study, pruritus was found in 49 patients (55.6 %); it was significantly associated with psoriasis (P = 0.001). In previous studies, pruritus was found in a higher percentage of patients.^{9,10} Due to their slower development, nail changes were of potential value in differentiating the underlying cause.^{11,12,13} Nail changes were observed in 72.7 % of cases. The most common nail change was subungual hyperkeratosis (61.3 %) followed by pitting (22.7 %). Palmoplantar keratoderma was seen in 62.5 % of patients. Both subungual

hyperkeratosis and palmoplantar keratoderma were commonest in psoriatic erythroderma and the association was statistically significant.

As reported by Eugster et al.¹⁴ five patients among seven with malignancy-related erythroderma had a history of pre-existing psoriasis. Khaled et al.¹⁵ observed nevirapine induced erythroderma in a well-known psoriatic patient. In the present study, nevirapine precipitated erythroderma in a patient with a past history of psoriasis and isoniazid in a patient with a history of ABCD. So, it is imperative to contemplate alternative aetiologies even in patients who may have a comprehensible history of pre-existing dermatoses.^{7,8,14}

Table 3 compares the etiological groups among the recent previous studies and the present study. Etiological factors depend largely on the population studied. Infections as aetiology are seen in countries like India due to environmental factors and poor living conditions.

Pre-existent dermatoses are generally of long duration^{4,16,17} and intractable to therapy. Boyd et al.¹⁶ observed an average of 14 years between the onset of psoriasis and erythroderma. In our study, erythroderma had occurred more frequently in patients with a history of psoriasis (22 / 40 cases). Furthermore, psoriatic patients had one or more relapses (14 / 40 cases). In patients with relapses, we have recorded a significantly longer duration of psoriasis with a mean of 2.5 years. So, longer the duration of psoriasis, the more is the risk of relapses.

Eczema is seen in 21.5 % of cases in our study. It may be due to greater exposure of sensitizers in our community when compared to developed countries. History of contact, pre-existing venous disease, distribution of original skin lesions pointed towards the aetiology of eczema.

Drugs as an etiologic group were seen in 10.2 % of cases. This is low in comparison to other studies.^{15,18,19} Despite widespread use or misuse and most of the medications being still available over the counter, drugs seem to be a lesser threat in our community. Drugs implicated in the present study are among the most commonly reported in the literature (phenytoin, isoniazid).

Infections as aetiology of erythroderma were seen in only a few studies.^{9,2} This was due to the differences in socio-economic and environmental factors. The primary contributing factors in contracting infections seem to be poverty and poor living conditions.

The incidence of malignancy induced erythroderma in our study was 4.5 %. There is a wide diversity in its incidence ranging from 1 % to 13 % in various studies.^{9,10,20,21,22,23} This incongruity seems to be connected to the frailty of investigative procedures and surveillance. The age group of patients of malignancy induced erythroderma in our study was younger range in two cases (28, 35 years) which is in contrast to other studies.¹⁵

In our study, despite an exhaustive screening, 14.7 % of patients could not be included in a precise aetiology (between 7.2 % and 46 % in the literature) (Table 3). These are categorized under idiopathic disorders and should be kept under close and continual surveillance. Patients with idiopathic erythroderma are many times elderly men (mean age of 64 years, sex - ratio of 6.6:1).²⁴ According to Wilson et al.¹⁴ some patients remit spontaneously, others are eventually identified as some other dermatosis. But, a noteworthy percentage of these patients will develop cutaneous T - cell

lymphoma (CTCL). Hence, idiopathic erythroderma is often regarded as a pre-malignant entity.

In the present study, a clinicopathological correlation was found in 64.6 % of patients. It was of maximum benefit in cases suspected to be related to pre-existing dermatoses and malignancy. The correlation varied between 59 and 74 % in various studies.^{15,22,25} Microscopic clues to diagnosis, if reviewed conventionally, can reveal primary aetiology. Walsh et al.²⁶ recommended that multiple serial biopsies from affected skin amplified the validity of the histopathologic diagnosis.

Relapses in our study were found in 20 patients (22.7 %). Hulmani et al.¹⁰ Khaled et al.¹⁵ found relapses in 10 % and 35.7 % in their studies. The highest number of relapses were found in psoriasis (15.9 %). This has been attributed to coexistent comorbidities, medication non-adherence and use of homoeopathic, Unani, ayurvedic, herbal and common home remedies.

The mortality rate in our study was 6.5 %. None of the 6 deaths could be attributed to erythroderma. Overall, the best prognosis was seen in the drug reaction and infection group in other studies, the recorded death rate varied from 18 to 64 %.^{6,17,19,27,28} Low mortality rate in the present study can be elucidated by a limited surveillance period.

CONCLUSIONS

Our study would ergo assist the view that erythroderma, although very troublesome to patients, in a majority of cases, is associated with a commending prognosis. Relapses constitute a great menace. Patients should be screened for barriers to medication non-adherence and counselled regarding the importance of taking drugs. Our study suggests a need for more effective comorbidity management and creating awareness regarding judicious use of drugs which can go far in preventing mortality and morbidity in erythroderma.

Limitations

The study has limitations. The true incidence of erythroderma in our population could not be determined as this was a cross-sectional study and no defined population group was available. Also, cases of erythroderma secondary to the cutaneous lymphoma may have been missed due to the lack of further follow-up.

Data sharing statement provided by the authors is available with the full text of this article at jemds.com.

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