



CLINICAL AND HISTOPATHOLOGICAL CORRELATION IN PATIENTS OF ERYTHRODERMA

Dermatology

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ABSTRACT

Background: Erythroderma also known as "exfoliative" dermatitis and "the red man syndrome" is characterised by diffuse erythema, scaling, pruritus and prolonged course affecting 90% or more of body surface area.

Methods: Fifty patients of erythroderma were evaluated at Government Medical College Amritsar for a period of one year to determine the aetiology, clinical features and histological changes. Clinical and histological findings were correlated.

Results: Male preponderance was present by 60%. Most of the patients were in the 2nd to 7th decade. Pruritus was present in most of the patients i.e. 35 [70%]. The most common clinical diagnosis of erythroderma was pre-existing dermatosis in 39 (78%) patients out of which, Air Borne Contact Dermatitis seen in 13 (26%) patients was the commonest dermatosis leading to erythroderma. The other common pre-existing dermatosis were psoriasis seen in 10 (20%) and atopic dermatitis in 8 (16%). Two patients each of pemphigus foliaceus, scabies and seborrheic dermatitis were noted while one patient each had photodermatitis and dermatophytosis. Drugs were the second commonest cause seen in 11 (22%) patients. Out of 50 cases 36 (72%) showed a good clinico histologic correlation while rest of the cases i.e. 14 (28%) did not correlate well.

KEYWORDS

clinical, histopathology, erythroderma, correlation

INTRODUCTION

Erythroderma is a syndrome characterised by diffuse erythema, scaling, pruritus and prolonged course [1]. This is also known as Exfoliative dermatitis and the "Red man syndrome". The term applies to any inflammatory skin disease involving the whole or most (>90%) of the skin surface. It is not a specific disease and can be seen both in benign and malignant diseases. The disease is usually insidious in onset except in staphylococcal scalded skin syndrome and drug induced erythroderma where the onset is abrupt and florid [2]. A dermatological condition that proved difficult to control in the past may develop into erythroderma during a dermatosis flare and in such cases aetiology is easy to reach. The diagnosis is difficult in a patient without any history of dermatological disease and who denies having recently taken any medication. According to Burton and Holden the aetiology of erythroderma is as follows [3]

chronic form is recognized by small scales [3]. Periorbital skin is inflamed and edematous causing ectropion and epiphora. Lymphadenopathy, hepatosplenomegaly, oedema feet and gynaecomastia may be observed [4]. Excessive protein loss through scaling, haemodilution due to increased plasma volume and hyper metabolism may contribute to hypoalbuminemia and severe oedema [5]. Furthermore, high output cardiac failure may occur at any time [6]. All cases should be considered as a dermatologic emergency and should preferably be hospitalized for treatment. The principles of management are to maintain skin moisture, avoid scratching and precipitating factors, apply topical steroids and treat the underlying cause and complications [7]. Once the acute phase is over, specific treatment can be undertaken. Histopathology is paramount and rewarding in 50% of cases if a diligent effort is made. Close followup of erythroderma of unknown cause by repeating skin biopsies can help to diagnose these patients [8]. Since erythroderma is a dermatological emergency accurate and prompt diagnosis is required to treat the patient. This study was undertaken to study the correlation between clinical and histopathological findings in patients of erythroderma.

Table 1: Aetiology of erythroderma

Hereditary	Ichthyosiform erythroderma Pityriasis rubra pilaris
Psoriasis	
Eczema (various types)	
Drugs	Especially organic arsenic, gold, mercury Occasionally penicillin, barbiturates etc
Pemphigus foliaceus	
Lymphoma and leukemias	
Other skin disease	Lichen planus Dermatophytosis Crusted scabies Dermatomyositis
Unknown (idiopathic)	
Rare causes include	Sarcoidosis Hailey Hailey disease Pemphigoid Toxic shock syndrome Lupus erythematosus Angioimmunoblastic lymphadenopathy Dermatomyositis Graft versus host disease

The patients of erythroderma show various clinical features eg. erythema, oedema, fever, malaise, shivering, lymph node enlargement, hepatosplenomegaly, hypothermia etc and laboratory abnormalities like raised WBC count, raised ESR and eosinophilia [2]. The acute form is heralded by formation of large scales, while the

AIMS AND OBJECTIVE

This study was based on following objectives

- To study the correlation between clinical and histological diagnosis.
- To study the correlation between clinical and histological improvement.

MATERIAL AND METHODS

Fifty cases of erythroderma were selected from Department of Skin and STD, Guru Nanak Dev Hospital, Government Medical College, Amritsar over a period of one year after taking the approval from Institutional Ethics Committee. All patients included in the study were clinically diagnosed cases of erythroderma selected from Skin and STD department of Guru Nanak Dev Hospital/Govt. Medical College, Amritsar. A detailed history and clinical examination was conducted and recorded on a special proforma. A complete dermatological examination of the whole body including mucous membranes was carried out and the patients were hospitalized whenever needed. Besides routine investigations like Haemoglobin estimation, complete blood count, ESR, FBS, SGOT, SGPT, blood urea, serum creatinine, total and differential serum proteins and complete urine examination, HIV antibody status (after pre informed consent) and PSA levels (in males wherever required) were determined. Special investigation in the form of skin biopsy was undertaken and subjected to histological studies in the department of Pathology, Government Medical College, Amritsar. Disease severity was assessed prior to the entry into the study and then fortnightly for eight weeks. At each assessment, the surface area involved estimated using the rule of nines [9]. Severity of

erythroderma was assessed according to the modified erythrodermic scores [10]. The severity of erythema, scaling and induration was recorded on a scale from 0 to 4. (0)- None, (1)-mild, (2)-moderate, (3)-severe, (4)-very severe. On overall assessment of erythema (E), scaling(S) and induration(I), each on the scale from 0 to 4 combined with percentage surface area involved determined the erythrodermic score, ranging between 0 to 100.

$$\text{Erythroderma score (ES)} = \frac{E + S + I}{12} * \text{Percentage body surface area}$$

Response to treatment was graded fortnightly and on completion of study on the basis of this score using the following categories: Grade I - <30% improvement in ES, Grade II - 30-60% improvement in ES, Grade III - 61-90% improvement in ES, Grade IV - >90% improvement in ES. Each patient was put on appropriate treatment and was followed up fortnightly upto period of remission or two months whichever was earlier. Skin biopsy was done during the early course of disease before initiation of therapy and during remission of disease at the end of trial at 8 weeks. In each case, a deep skin biopsy was taken from skin of back of the trunk. After cleaning the area with betadine and methylated spirit, local anaesthesia with 2 ml of 2% xylocaine was infiltrated. With the help of Bald Parker Knife, an elliptical tissue was taken about 1 cm X 0.5 in size. Stitches were applied to bring the edges close and stop bleeding. The biopsy tissue was immediately put in a vial containing 10% formalin. After keeping it overnight in a fixative, this was processed in automatic tissue processor where four changes (one hour each) of the ascending concentration of acetone were given. Clearing of the tissue was done in three subsequent changes of xylene. Tissue was embedded in paraffin wax and blocks were made. Thin paraffin sections of 3-4µ in thickness were cut and stained with haematoxylin and eosin.

RESULTS

Out of 50 cases the maximum number of cases i.e. 42 (84%) were between 2nd to 7th decade and only 3 (6%) were below 20 years of age. Five (10%) patients were above the age of 80 years. The youngest patient was of 11 years and oldest was 100 years of age.

Table 2: Showing age wise distribution in patients of erythroderma

Age group	Number of cases	Percentage
<20	3	6
>20-40	12	24
>40-60	17	34
>60-80	13	26
>80	5	10
Total	50	100

Males predominated females by 60% and male/female ratio was 4:1.

Table 3: Showing sex distribution in patients of erythroderma

Sex	Number of cases	Percentage
Male	40	80
Female	10	20
Total	50	100

Table 4: Showing duration of disease

Duration	Number of cases	Percentage
<1 month	9	18
>1 month- 6 months	19	38
>6 months - 1 year	10	20
>1 year- 5 years	7	14
>5 years	5	10
Total	50	100

Table 5: Showing salient clinical signs and symptoms at the time of reporting

Salient features	Number of cases					
	Males		Females		Total	
	No.	%age	No.	%age	No.	%age
Pruritus	27	54	8	16	35	70
Hyperthermia	3	6	1	2	4	8
Hypothermia	2	4	1	2	4	8
Tachycardia	5	10	3	6	8	16
Pedal oedema	14	28	3	6	17	34

Generalised lymphadenopathy	11	22	2	4	13	26
Hepatomegaly	6	12	1	2	7	14
Nail changes	12	24	2	4	14	28
Mucosal involvement	8	16	1	2	9	18

Pruritus was present in most of the patients i.e. 35 [70%]. Other patients reported a burning or stinging sensation and tightness of the skin. Hypo and hyperthermia was present in 4 (8%) and 3 (6%) of the patients respectively at time of reporting.

Table 6: Showing clinical diagnosis of patients of erythroderma

Cause	Number of cases					
	Males		Females		Total	
	No.	%age	No.	%age	No.	%age
Drugs	9	18	2	4	11	22
Pre existing dermatosis						
Psoriasis	8	16	2	4	10	20
ABCD	10	20	3	6	13	26
Atopic dermatitis	7	14	1	2	8	16
Pemphigus foliaceus	1	2	1	2	2	4
Scabies	2	4	-	-	2	4
Dermatophytes	1	2	-	-	1	2
Photodermatoses	-	-	1	2	1	2
Seborrheic dermatoses	2	4	-	-	2	4
Total	40	80	10	20	50	100

The most common clinical diagnosis of erythroderma was pre-existing dermatosis in 39 (78%) patients out of which, Air Borne Contact Dermatitis seen in 13 (26%) patients was the commonest dermatosis leading to erythroderma. The other common pre-existing dermatosis were psoriasis seen in 10 (20%) and atopic dermatitis in 8 (16%). Two patients each of pemphigus foliaceus, scabies and seborrheic dermatitis were noted while one patient each had photodermatoses and dermatophytosis. Drugs were the second commonest cause seen in 11 (22%) patients. History of drug intake was present in 31 patients in the form of tablets or local application, but only in 11 cases, the clinical presentation correlated with drug induced erythroderma.



Figure 1: (a) and (b) Patient of erythroderma due to psoriasis



Figure 2: (a) and (b) Patient of drug induced erythroderma

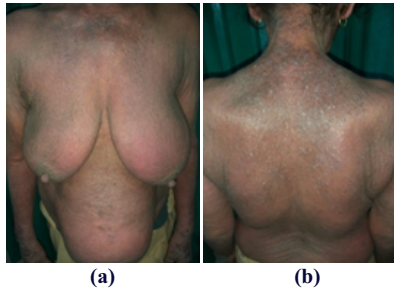


Figure 3: (a) and (b) Patient of erythroderma due to Air Borne Contact Dermatitis

Table 7: Showing laboratory investigations of patients of erythroderma

Investigations	Number of cases					
	Males		Females		Total	
	No.	%age	No.	%age	No.	%age
Anaemia	26	52	6	12	32	64
Elevated ESR	10	20	-	-	10	20
Eosinophilia	14	28	1	2	15	30
Lymphocytosis	8	16	1	2	9	18
Lowered serum proteins	5	10	2	4	7	14
Elevated liver enzymes	5	10	-	-	5	10
Skin scrapping						
-Mite	2	4	-	-	2	4
-Fungus	1	2	-	-	1	2
ELISA for HIV	1	2	-	-	1	2

Microcytic hypochromic anaemia was observed in 32 (64%) patients. ESR in 10 (20%) patients was above 20 mm in 1st hour. This was found in patients above the age of 70 years, with chronic dermatitis and in the drug induced group. Eosinophilia was recorded in 15 (30%) patients. Lymphocytosis was present in 9 (18%) patients, lowered S.proteins were recorded in 7 (14%) patients and abnormal liver function in 5 (10%) patients. This was seen mainly in alcoholic patients and in the drug induced group. Skin scrapings for scabies were positive in 2 (4%) patients and for fungus in 1 (2%) patient. One patient was found to be positive for HIV (AIDS).

The most common histology findings were that of drug induced

Table 10: Showing histopathological changes in patients of erythroderma

Histologic findings	Drug induced (n=20)		Psoriasis (n=6)		Chronic dermatitis (n=20)		Lichen planus (n=1)		PMLE (n=1)		Non specific (n=2)	
	No.	%age	No.	%age	No.	%age	No.	%age	No.	%age	No.	%age
EPIDERMAL												
Hyperkeratosis	11	55	6	100	13	65	-	-	1	100	2	100
Parakeratosis	11	55	5	83	8	40	-	-	-	-	1	50
Thinning of granular layer	-	-	-	-	-	-	1	100	-	-	-	-
Acanthosis	9	45	1	16	10	50	-	-	-	-	-	-
Spongiosis	8	40	1	16	3	15	-	-	-	-	-	-
Bulla formation	1	5	-	-	-	-	-	-	-	-	-	-
Cleft formation	5	25	-	-	-	-	-	-	-	-	-	-
Elongation of rete ridges	2	10	6	100	-	-	-	-	-	-	-	-
Neutrophils	1	5	6	100	-	-	-	-	-	-	-	-
Basal layer												
-liquifactive degeneration	-	-	-	-	-	-	1	100	-	-	-	-
-vacuolar degeneration	1	5	-	-	-	-	-	-	-	-	-	-
-pigment	1	5	-	-	2	10	-	-	-	-	-	-
DERMAL												
oedema	7	35	-	-	1	5	-	-	1	100	-	-
Lymphocytic infiltrate	12	60	3	50	20	100	1	100	1	100	2	100
Eosinophils	10	50	-	-	7	35	-	-	1	100	-	-
Neutrophils	6	30	3	50	1	5	-	-	1	100	-	-
Perivascular infiltration	12	60	3	50	6	30	-	-	1	100	1	50
Melanophages	2	10	-	-	1	5	1	100	-	-	-	-
Proliferation of blood vessels	4	20	1	16	4	20	-	-	-	-	-	-
Plasma cells	-	-	-	-	2	10	-	-	-	-	-	-

dermatitis and chronic dermatitis i.e. 20 (40%) patients each, followed by psoriasis 6 (12%) patients, 1 (2%) each of lichen planus and PMLE and 2 (4%) patients had a non-specific histology. The maximum number of males were in the drug induced group and females in the chronic dermatitis group.

Table 8: Showing histopathological diagnosis in patients of erythroderma

	Clinical diagnosis	Histologic diagnosis	Correlation
11 (22%)	Drug induced	Drug induced	Yes
7 (14%)	Psoriasis	Psoriasis	Yes
9 (18%)	ABCD	ABCD	Yes
6 (12%)	Atopic dermatitis	Chronic dermatitis	Yes
1(2%)	Photodermatitis	PMLE	Yes
2 (4%)	Seborrheic dermatitis	Chronic dermatitis	Yes
4 (8%)	ABCD	Drug induced	No
1 (2%)	Scabies	Chronic dermatitis	No
1 (2%)	Scabies	Non specific	No
1 (2%)	Pemphigus foliaceus	Chronic dermatitis	No
1 (2%)	Atopic dermatitis	Lichen planus	No
1 (2%)	Atopic dermatitis	Drug induced	No
2 (4%)	Psoriasis	Drug induced	No
1 (2%)	Tinea incognito	Non specific	No
1 (2%)	Psoriasis	Acute irritant dermatitis	No

Out of 50 cases, 36 (72%) cases showed a good clinico histologic correlation while rest of the cases i.e. 14 (28%) did not correlate well.

Table 9: Clinicohistologic correlation in biopsy sections of erythroderma

Histologic diagnosis	Number of cases					
	Males		Females		Total	
	No.	%age	No.	%age	No.	%age
Drug induced	17	34	3	6	20	40
Psoriasis	5	10	1	2	6	12
Chronic dermatitis	15	30	5	10	20	40
Lichen planus	1	2	-	-	1	2
PMLE	-	-	1	2	1	2
Non specific	2	4	-	-	2	4

Table 11 : Showing correlation between clinical and histologic improvement in 34 cases

Diagnosis	Histology on admission	Histology after treatment	Improvement
Drug induced	Hyperkeratosis Parakeratosis Acanthosis Spongiosis Elongation of rete ridges Cleft formation at basal layer Neutrophilic exocytosis Dermal oedema and infiltrate	Epidermis normal Inflammatory infiltrate reduced	Yes
Psoriasis	Hyperkeratosis Parakeratosis Acanthosis Spongiosis Elongation of rete ridges Neutrophils in corneal layer Dermal edema and infiltrate	Hyperkeratosis reduced Parakeratosis reduced Inflammatory cells reduced	Yes
Chronic dermatitis	Hyperkeratosis Parakeratosis Acanthosis Spongiosis Elongation of rete ridges Dermal infiltrate	Epidermis normal Dermal infiltrate reduced	Yes
PMLE	Patchy hyperkeratosis Dermal oedema	Epidermis normal Dermal infiltrate reduced	Yes
Non specific	Hyperkeratosis Parakeratosis Minimal lymphocytic infiltrate in dermis	Epidermis normal Infiltrate reduced	yes

In this study 50 section of biopsies were viewed before the commencement of treatment and after administering treatment patients were examined every 15 days for 2 months. After this period, a repeat biopsy was undertaken. Some of the patients refused repeat biopsy after treatment, so we were able to do repeat biopsies in 34 cases only. The improvement was mainly seen in cases of drug induced, chronic dermatitis, PMLE and nonspecific cases with slight improvement in psoriasis in the form of normalization of the epidermis, rete ridge pattern and reduction in the inflammatory infiltrate after treatment. Each of the patient was put on treatment which included general treatment, topical and systemic therapy and specific treatment in relation to the underlying pathology.

Table 12: Showing response of erythrodermic patients to treatment.

Number of patients	ES before treatment	Erythrodermic score (ES) after treatment							
		15 days		30 days		45 days		60 days	
		ES	Grade	ES	Grade	ES	Grade	ES	Grade
3	60-70	50-60	I	30-50	II	10-30	III	<10	III
4	71-80	61-70	I	40-60	II	20-40	III	<20	III
11	81-90	71-80	I	50-70	II	30-50	III	<30	III
								<10	IV
32	>90	81-90	I	60-80	II	40-60	II	<40	III
								<10	IV

In this study response to treatment was assessed according to the erythrodermic scores of the patients and fortnightly percentage improvement in their scores was compared to previous score. Maximum number of patients i.e. 32 had an initial erythrodermic score more than 90 and after treatment their scores showed improvement up to grade III (60-90/0) in 8 patients and grade IV (>90%) in 24 patients. 11 patients had erythrodermic score between 81-90 and these also showed grade (60-90%) and IV (>90%) improvement after 2 months. Four patients had erythrodermic score of 71-80 and 3 had a score of 60-70. Both these groups showed improvement upto grade III (60-90%) after treatment. The grade IV improvement was seen in the drug induced group and some cases of chronic dermatitis.

DISCUSSION

Exfoliative dermatitis has been a frequent topic of study since the first description by Hebra in 1868[11]. The present study was undertaken to

study the various clinical and histopathological skin changes in patients of erythroderma and to study the correlation between clinical and histologic diagnosis. In our study we observed the incidence of erythroderma between 11 years to 100 years of age whereas Vasconcellos et al found the age of presentation between 16 to 60 years [1]. The higher age incidence in our study could be due to constitutional, geographic and social circumstances.

Males predominated females by 60% with male to female ratio to be 4:1 which was similar to the results of a study by Botella Estrada al[8], whereas other authors have reported male to female ratio to be 2.3: 1 and 2.25:1 respectively [12]. Although our findings are slightly higher than reported over some authors, but are much lower as compared to the reported ratio of 11: 1 [13].

Out of 50 cases, 35 (70%) cases were from rural background and 15 (30%) only were from the urban background. Punjab being an agricultural state has got maximum population in rural areas as compared to urban area. Our institute being of tertiary level, patients were referred when their condition either did not improve or flared up in spite of treatment and this explains the majority of cases from rural areas. This also explains increased incidence of Air borne contact dermatitis as there is increased exposure to plant antigens. The duration of erythroderma varied from a few days to years. The patients of drug induced erythroderma had a shorter duration while those of pre-existing dermatosis like, airborne contact dermatitis, atopic dermatitis and psoriasis had longer duration. All the patients presented with a wide range of local and systemic findings. Pruritus was the most common complaint and it was present in 70% of the patients. It was also the most common feature in the study conducted by Pal and Haroon [14]. Mucosal lesions such oral erosions, pigmentation, angular cheilitis, oral candidiasis, conjunctivitis, nasal crusting and erythema over glans was noticed in 9 patients. The mucosal changes were more common in drug induced erythroderma whereas changes were generalized and not specific for any lesion except pitting in psoriasis. Similar mucosal as well as nail changes have been reported by Pal and Haroon [14].

Pre-existing dermatosis were the most common cause of erythroderma in our study. In this group maximum number of cases i.e. 13 (26%) were diagnosed as air borne contact dermatitis, 10 (20%) with psoriasis and 8 (16%) with atopic dermatitis. Drugs were found to be the second most common cause recorded in 11 (22%) patients, the main culprit being carbamazepine, anti-tubercular drugs and steroid withdrawal. The results were similar to a study conducted by Chiratikamwong [12], who found pre-existing dermatosis to be the most common cause of erythroderma followed by drugs, mainly anti tubercular drugs, NSAIDS, antidiabetics, dilantin and allopurinol. Within the dermatosis group, psoriasis was commonest.

Further, it was noted that the patients with pre existing dermatosis like air borne contact dermatitis, psoriasis and atopic dermatitis, relied more on indigenous and self-medications so specific treatment was often delayed and they landed up in erythroderma often. Also the indiscriminate use of drugs like NSAIDS, antibiotics and steroids by non-dermatologists in such cases not only lead to inadequate cure but also an increased incidence of drug reactions.

The laboratory findings showed a hypochromic anaemia in 32 patients and raised ESR in 10 patients. The raised ESR was seen in patients on anti tubercular treatment, patients above the age of 70 years and those with chronic dermatitis. Eosinophilia and lymphocytosis were noted in 15 and 9 patients while 7 patients had lowered serum proteins and 5 patients had abnormal liver function tests. These were seen in alcoholics and in the drug induced group. Anaemia was common in patients which could be related to the improper diet and lack of awareness in the rural patients. In general, these were non-contributory to the determination of aetiology and only occasionally did they suggest the etiological basis for erythroderma. However they did help us in management and prognosis of the patients of erythroderma.

It was noticed that drug reactions and inflammatory skin diseases including spongiotic dermatitis and psoriasis were the two main groups responsible for the majority of the cases of erythroderma. The most frequent changes in epidermis were hyperkeratosis, parakeratosis, acanthosis and spongiosis. The dermal changes were mainly in the form dermal oedema, lymphocytic infiltration with eosinophils and neutrophils in some of the sections. A perivascular

infiltrate was also noticed in most of the sections. The histopathology of exfoliative dermatitis often reveals a non-specific picture consisting of orthokeratosis (hyperkeratosis, parakeratosis), acanthosis and a chronic perivascular inflammatory infiltrate with or without eosinophils [2]. In addition to the above mentioned changes, other changes noted in were cleft formation and necrotic keratinocytes in the drug induced group while elongation of rete ridges was seen in the psoriasis and dermatitis groups. Furthermore, neutrophils were present, in the stratum corneum (Munro's microabscess) in sections consistent with diagnosis of psoriasis. Basal layer showed liquefactive degeneration in the section of Lichen planus and vacuolar drug induced erythroderma. Pigment was increased in the drug induced group. In the dermis, proliferation of blood vessels, presence of melanophages and plasma cells were other findings. In other studies importance of a lichenoid interface dermatitis has been stressed. It follows that the lichenoid infiltrate in a biopsy from an erythrodermic patient should arouse suspicion of either lymphoma or an eruption. It is likely that these interface changes in retrospective may represent basal epidermotropism [15]. We did not encounter such findings in our sections but it can be inferred that the patients of erythroderma, do require multiple, serial biopsies in order to rule out such changes. They should also be followed up for as long as possible.

Eosinophils have been thought to be present in drug eruptions, spongiotic dermatitis and in mycosis fungoides. We did not find any changes suggestive of cutaneous T-cell lymphoma or mycosis fungoides in any of the sections. Previous works in this field had shown that difficulties sometimes arise in distinguishing between the basal epidermotropism which characterized cutaneous T-cell. It can be concluded from our study and previous studies that the various findings on histology were subtle, but were, helpful in reaching the diagnosis in some cases, when related clinically. Although, the biopsy findings were not very specific careful evaluation lead to the diagnosis in most of the cases. There was a definite improvement in the histology pictures observed in the sections. This showed a correlation of the effect of treatment not only clinically but also histologically. Histopathological changes in the skin are variable and skin biopsy is an important investigation which can guide us to the correct diagnosis. As management of each case depends on the cause, correct diagnosis will decide the course of treatment.

CONCLUSION

The experience from the study concludes that erythroderma, although a distressing disorder, is a treatable condition. But the main challenge lies in identifying the underlying cause and managing it. Skin biopsy is the gold standard procedure. It is likely that its value will further improve with advancement of knowledge in realm of dermatopathology.

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