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RESEARCH ARTICLE

ERYTHRODERMA : STUDY OF CLINICO- ETIOLOGY AND COMPLICATIONS FROM WESTERN INDIA

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ABSTRACT

Background : Erythroderma is extreme state of skin irritation involving more than 90 percent of skin surface area having many underlying causes.
Aim: 1. To check for epidemiological factors in erythroderma. 2.To study clinical features of erythroderma. 3. To identify the aetiology of erythroderma. 4. To describe the complications of erythroderma
Materials and Methods: This study was performed at the department of dermatology in a tertiary care hospital of Western India. We studied 31 cases of erythroderma for epidemiology, clinical features, clinical course and complications. Clinico-pathological correlation was done for aetiology of erythroderma.
Statistical method used : student t test unpaired and chi square test
Results: The mean age of onset was 43.99 years with a male to female ratio of 2.1:1. The clinical features found were redness, scaling, pruritus, fever, chills, lymphadenopathy and edema. On clinicopathological correlation the most common aetiology found was psoriasis vulgaris, (35.48%). This was followed by drug (included both drug induced erythroderma and DRESS syndrome) (22.5%). Remaining cases belonged to dermatitis (16.12%) (Contact dermatitis (two), photoallergic dermatitis (three)), and 6.45% (n=2) patients belonged to each of pemphigus foliaceus, NBIE, paraneoplastic dermatomyositis and generalised pustular psoriasis. Complications like hypoproteinemia (45.16%), electrolyte imbalance (45.16%), temperature dysregulation (22.5%) and secondary infection (32.25%) were observed.
Limitations : Follow up of cases was not studied to know the long term sequel.
Conclusion: Clinical features were identical irrespective of aetiology. Detailed clinic-pathological examination helps to establish the aetiology of erythroderma. Monitoring of vitals and biochemical parameters is essential for early diagnosis of complications and its management.

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INTRODUCTION

Erythroderma represents an extreme state of skin irritation involving more than 90 percent of skin surface area that can be fatal, primarily because of its metabolic burden and complications like infections, fluid and electrolyte imbalance, thermoregulatory imbalance, high output cardiac failure and acute respiratory distress syndrome (Okoduwa, 2009 and Sehgal, 2004). The prognosis of erythroderma is determined by its underlying cause. Hence knowing the aetiopathogenesis facilitates precise management (Sehgal, 2004). A detailed outline of the patient's history to elicit possible triggering events should be determined.

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Its management continues to be a challenge due to its multiple aetiologies. A study of the clinical features and aetiology of erythroderma will help us in giving proper treatment along with adequate supportive measures thus reducing morbidity and mortality associated with disease course.

MATERIALS AND METHODS

The study was descriptive, prospective, observational, single centre study in tertiary care institute. Study duration was 16 months. Study population were patients of Erythroderma admitted in our hospital. Duly signed informed consent form was filled. Using convenience sampling method, 31 patients were enrolled in our study. Patients with erythroderma refusing indoor management were excluded. Permission from institutional ethics committee was obtained. Epidemiological factors of patients were recorded which included age, sex, and

occupation. Patients were clinically evaluated with detailed history and complete physical examination. History included onset and evaluation of disease, aggravating factor, any associated systemic disorders, previous skin disorders and drug intake. Based on duration of erythroderma from onset till day of admission, erythroderma was classified as acute and chronic type. Patients with duration of presentation ≤45 days were classified as acute and >45 days were classified as chronic. Patients were examined for general condition including vital parameters and detailed clinical cutaneous and systemic findings. Detailed laboratory investigations were done in all cases and few special investigations as per needs of individual case. Study participant characteristics were described using descriptive statistics. Continuously distributed variables were described using mean± standard deviation and categorical variables by percentage and frequency of distribution. Statistical test used were student t test unpaired and chi square test. Difference was considered significant when p value was less than 0.05.

RESULTS

The mean age affected was 43.99 years (range = three months-72 years). Maximum patients belonged to age group 41-60 year (35.48%). Male to female ratio was 2.1:1. Four cases belonged to paediatric age group (0-12 years). The mean age of onset in them was 2.6 years. Erythroderma occurred later in men(mean 49.8 years) than in women (mean 31.6 years). On comparing the mean age, calculated p value is 0.02 which is statistically significant (p<0.05%). Of five patients diagnosed with erythroderma secondary to dermatitis four were in occupation {gardener(one), farmer(two), painter(two)} which could aggravate contact dermatitis. A significant statistical association was present between the occupational exposure and erythroderma secondary to dermatitis(p<0.001). Itching was reported by 87.1% patients.

Pre-existing dermatoses was present in 54.83 % patients which included chronic plaque psoriasis (25.8%), Non bullous ichthyosiform erythroderma (NBIE) (6.45%), pemphigus foliaceus(6.45%) and dermatitis(16.19%). Fair general condition was seen in 74.2% and poor in 25.8% of cases. Input output balance was positive (input-output>650 ml) in 48.38%, negative in 32.25 % (input-output<500ml) and normal (input-output=500-650ml)) in 19.35%. Hyperthermia (>36.7^{0}C) was seen in 54.8% and hypothermia (<35.9^{0}C) in 6.45% patients. Eighteen patients had tachycardia (pulse rate> 100) and seven patients had tachypnea (> 20 breaths per minute). These patients had fever with associated secondary infection and sepsis. Normal arterial blood pressure was seen in 93.5% cases. Pallor was present in 48.38% cases, lymphadenopathy in 22.5% patients and bilateral pitting pedal edema in 61.2 % of patients. Weakness of proximal muscle of upper extremities (power =3/5 by MRC grading) was seen in 6.45% of patients with paraneoplastic dermatomyositis. Mucosa was involved in form of erosions in 12.9% of cases. Palmar involvement was present in 67.74 % of cases and soles were involved in 58.06% of cases in form of scaling, erythema, and fissuring. Various nail changes observed are summarised in Table 1.

Table 1. Nail changes

Nail changes	Percentage
Ebonisation	35.5%
Ridging	29%
Subungual hyperkeratosis	29%
Pitting	25.8%
Onychodystrophy	12.9%
Beau's line	9.1%

Anaemia was seen in 74.2% (n=23) cases (haemoglobin<12 g/dl for males and <11 g/dl for females). Microcytic type of anaemia was seen in sixteen cases, macrocytic type in one and normocytic in six cases.

Table 2. Specific findings on biopsies confirming the aetiology

Aetiology	Histopathologic diagnosis	Clinical Diagnosis	Percentage of patients with positive histopathologic diagnosis	Specific findings on histopathology
Psoriasis	7	11	63.63%	Parakeratosis, Elongation of rete ridges, suprapapillary thinning, dilatation of superficial dermal blood vessels
Generalised pustular psoriasis	2	2	100%	Subcorneal blister, Kogoj spongiform pustule, eosinophilia infiltrate in dermis
Contact dermatitis	2	5	40%	Spongiotic dermatitis with infiltration of eosinophils in epidermis
Pemphigus Foliaceus	2	2	100%	Intraepidermal blister ,spongiosis, acantholytic cells
Paraneoplastic dermatomyositis	2	2	100%	Vacuolation of basal layer, interface dermatitis, mucin deposition in dermis
DRESS syndrome	3	3	100%	Parakeratosis, basal cell vacuolization, lichenoid interphase dermatitis, perivascular lymphocytic infiltrate and eosinophils
Drug induced erythroderma	2	4	50%	Parakeratosis, necrotic keratinocytes, basal cell vacuolization, perivascular lymphocytic infiltrate and eosinophils
Non bullous ichthyosiform erythroderma	0	2	Nil	nil

Two paediatric patients (age: three months and two and half years) and two adult patients with pemphigus foliaceus did not report itching. Other symptoms noted were generalised redness (100%), generalised scaling (93.5%), chills (71%) and fever (54.8%). Acute erythroderma was present in 54.83% patients and chronic in 45.16% patients. Aggravating factors were present in 51.61% of patients (Figure 1).

Erythrocyte sedimentation rate (1-10 mm/hr) was raised in 51.61% patients. Leukocytosis (4000-10,000 cu.mm) was seen in 51.61% of patients. Neutrophilia (50-60%) was seen in 41.93% cases and eosinophilia (2%-6%) was seen in 35.5% of cases. Blood Urea Nitrogen (7-20 mg/dl) and Serum Creatinine (1-2 mg/dl) were raised in two patients. One patient had drug induced erythroderma in whom decreased oral intake of fluid

lead to dehydration and pre-renal failure which normalised with adequate fluid infusions. Other patient had chronic kidney disease in whom levels remained elevated post resolution of erythroderma. Serum uric acid (2.5-7 mg %) was elevated in 16.12% and Serum calcium (9-10.5 mg/dl) was decreased in 12.9% of patients. Hyponatremia (normal =132-144 meq/L) was seen in 45.16% and hyperkalemia (normal: 3.5-4.5 meq/l) in 9.67% patients. Hypoproteinemia (normal: 5-7.5 gm %) was present in 45.16% patients. Aspartate transaminase and Alanine transaminase (normal :5-40 IU/L) were elevated in 16.12% of cases with aetiology of Drug rash with Eosinophilia and Systemic Symptoms syndrome(DRESS) (9.1%) and paraneoplastic dermatomyositis (6.45%).

E.coli was seen in 6.45% patients. One patient showed bacteraemia with coagulase negative staphylococcus aureus. Organisms grown on culture of scales are shown in Figure 3.

DISCUSSION

It is seen that males are twice more commonly affected than females. This is concordance with earlier studies that have shown a ratio between 2:1 and 4:1 (Pal, 1998; Vasconcellos, 1995; Chaudhary, 1997). The age group affected maximally was 41-60 years, which is in concordance to study by Sehgal *et al* (Sehgal, 1986).

Table 1. Comparison of histopathologic correlation with other studies

	Our study	Kondo *et al* (2006)	Hulmani *et al* (2014)	Pal and Haroon (1998)	Cesar *et al* (2016)	Khaled *et al* (2010)	Banerjee *et al* (2015)
Patients biopsied	30	51	30	51	95	45	32
Conclusive histopathological correlation	66.66%	72.54%	80%	27.7%	66.3%	64.6%	59.3%

Table 2. Comparison of aetiology with other studies

Study	Pal *et al* (1998) (n=90)	Hulmani *et al* (2014) (n=30)	Bandopadhyay *et al* (1999) (n=75)	Cesar *et al* (2016) (n=103)	Shirazi *et al* (2015) (n=58)	Present study (n=31)
Psoriasis	37.8%	33.33%	33.33%	44.7%	17.2%	41.93%
Eczema	12.2%	20.0%	4.0%	16.5 %	6.8%	16.12%
Ichthyosis	7.8%	0	1.33%	16.5%	0%	6.45%
PRP	2.2 %	3.3%	5.33%	0	3.4%	0%
Scabies	2.2%	0	1.33%	1.0%	0%	0%
Pemphigus Foliaceus	5.6%	0	5.33%	1.0%	0%	6.45%
Lichen Planus	0	0	0	0	3.4%	0%
Drug reactions	5.5%	16.6%	12%	18.4%	32.7%	22.5%
Atopic Dermatitis	0	6.6%	13.3%	0	20.6%	0%
Malignancy	5.5%	3.3%	2.67%	12.6%	3.4%	0%
Other Dermatitis	6.6%	0	0%	1%	1.7%	6.45%
Idiopathic	14.6%	16.6%	21.33%	3.9%	10.3%	0%

Table 3. Japanese group's criteria (Choudhary *et al*., 2013)

1.	Maculopapular rash developing >3 weeks after starting with the suspected drug.
2.	Prolonged clinical symptoms 2 weeks after discontinuation of the suspected drug.
3.	Fever >38°C
4.	Liver abnormalities (alanine transaminase>100U/L)
5.	Leukocyte abnormalities
6.	Leukocytosis (>11 X 109/L)
7.	Atypical lymphocytosis (>5%)
8.	Eosinophilia (>1.5 x 109 /L)
9.	Lymphadenopathy
10.	Human Herpes 6 reactivation
	The diagnosis is confirmed by the presence of atleast 7 criteria (typical DHS).

Skin biopsy was performed in 30 patients as one patient denied consent. In 66.66% cases, specific findings on biopsies helped in correlating and confirming the aetiology of erythroderma (table 2), while 33.33 % patients showed nonspecific changes on histopathology which did not correlate with the aetiology.

On clinicopathological correlation the aetiologies found are shown in Figure 2. In paediatric age group, the aetiologies are psoriasis vulgaris(two), generalised pustular psoriasis (one) and NBIE(one). The most common aetiology was psoriasis vulgaris in both children and adults. The most common drug implicated was phenytoin. Complications like temperature dysregulation, hypoproteinemia, electrolyte imbalance and secondary infection were observed. Secondary infection was seen in 32.25% patients. The most common form of secondary infection seen was superficial skin infection (22.5%) diagnosed on pus culture with most common organism being Pseudomonas aeruginosa (12.9%). Urinary tract infection with

Occupational exposure of allergen is known to cause contact dermatitis which progresses to erythroderma (Sasseville, 2014). This aspect needs to be considered in depth for elimination of causative factor of erythroderma. Clinical improvement was noted when patients were kept away from source of allergen. Irrespective of aetiology, clinical features of erythroderma were almost identical. Redness was found to be most common symptom followed by scaling and pruritus. Erythema was followed by scaling over four to five days. These findings are similar to other studies (Sehgal, 1986; Hulmani, 2014 and Kimgai, 2003). The most common aggravating factor noted was winter season in patients with psoriatic erythroderma and non bullous congenital ichthyosiform erythroderma followed by injudicious use of steroids and topical applications which can cause irritant injury leading to koebnerization thus aggravating erythroderma (Hulmani, 2014). Pre-existing dermatoses was

present in 54.83% cases as compared to study by Cesar *et al*. (César, 2010), where it was present in 65% cases. This difference from western study could be due to lack of awareness about the disease amongst the population and inadequate resources and facilities at peripheral health centre to diagnose the condition. Psoriasis was most common pre-existing dermatoses. This is in concordance with many studies (Sehgal, 1986; Shirazi, 2015; Li, 2012; Sigurdsson, 1996). Injudicious use of steroids and irritants by quacks without making a proper diagnosis of the skin condition could be one of the reason for psoriasis to precipitate into erythroderma.

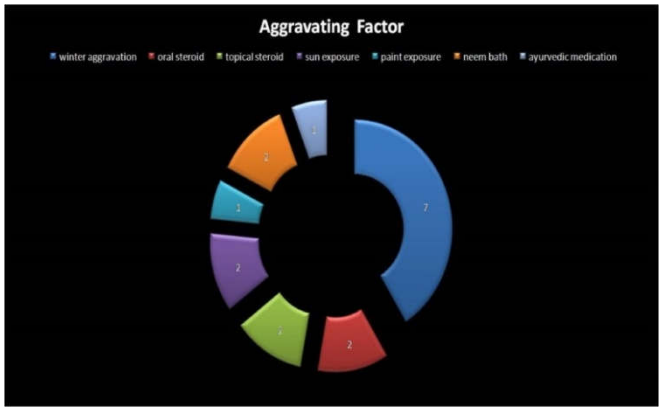

Figure 1. Aggravating factors

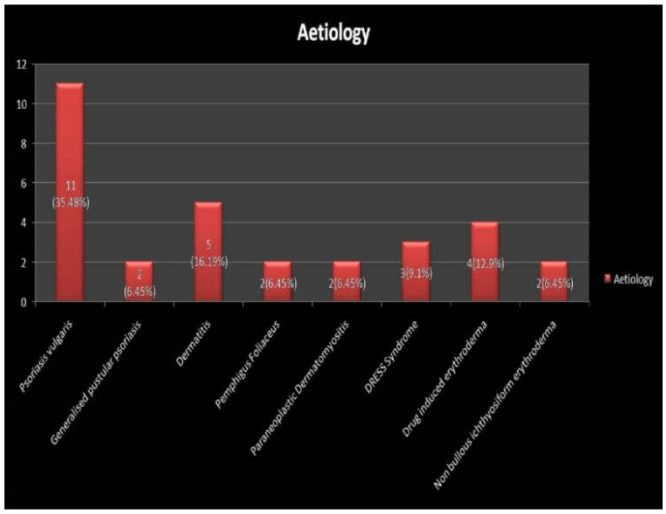

Figure 2. Aetiology of erythroderma

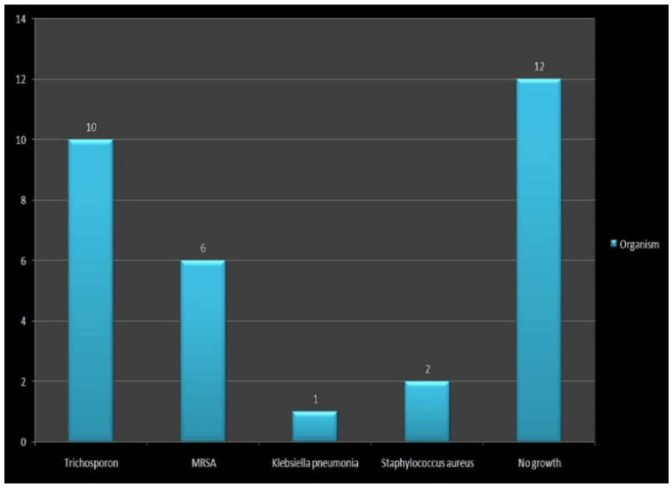

Figure 3. Organisms grown on scale culture

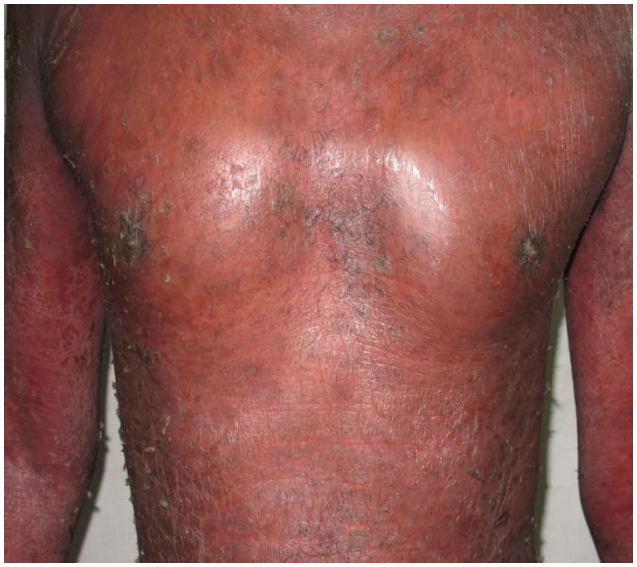

Figure 4. Bright red erythema with scaling

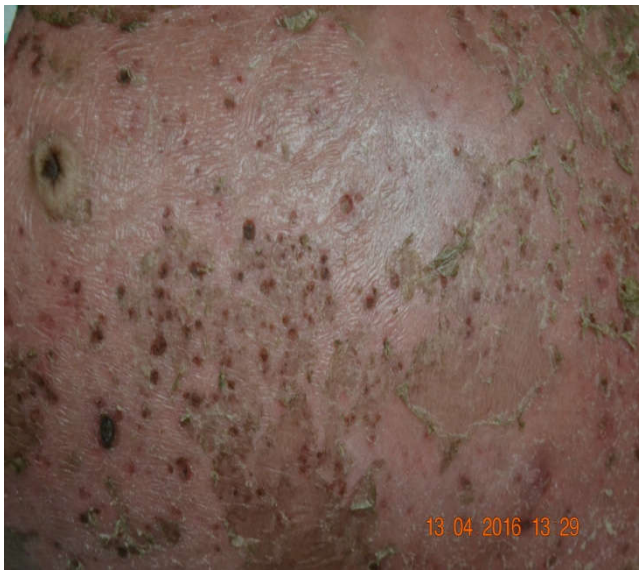

Figure 5. Erythroderma secondary to generalised pustular psoriasis

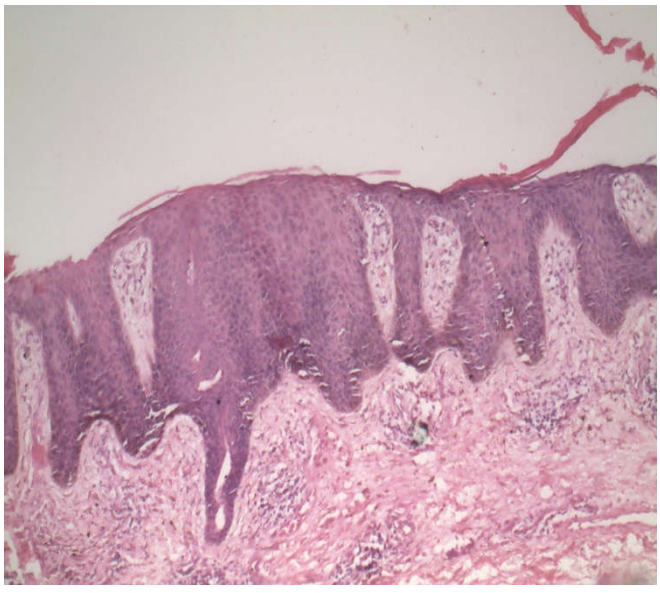

Figure 6. Drug induced Erythroderma (H and E, 40X) Necrotic keratinocytes along with interphase dermatitis

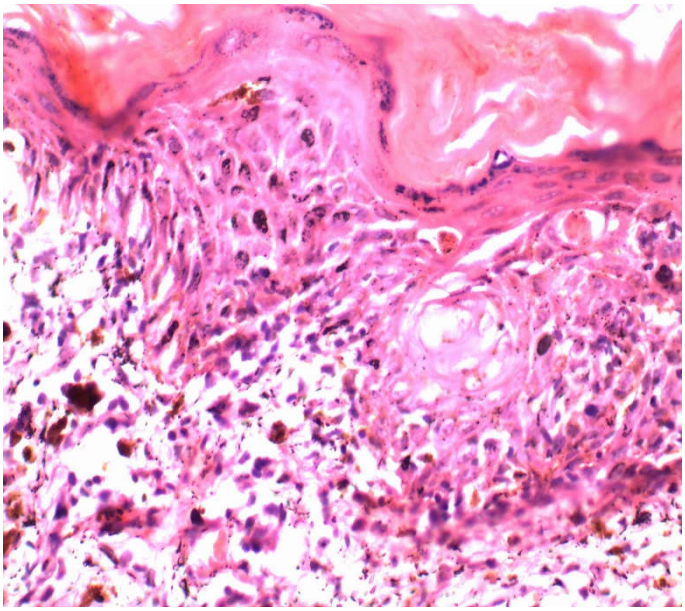

Figure 7. Psoriasis (Hand E,10X) : Psoriasiform hyperplasia with suprapapillary thinning with dilatation of superficial capillaries

Input output balance is difference between the total fluid input (oral + parenteral) and total fluid output during a day (urine + faeces + insensible fluid loss through skin) (Langford, 2000). A positive input output balance indicates input of fluid > output of fluid. Due to increased insensible water losses body tries to conserve water with decreased urine output, thus input becomes greater than output. Thus fluid should be given conservatively to prevent the overload. Similarly a negative input output balance indicates output of fluid > input of fluid. This occurs in uncompensated fluid loss, sepsis and decreased input of fluid. Adequate fluid replacement is needed to prevent dehydration. Tachycardia and tachypnea can be explained due to fever, sepsis, hypovolemia and increased basal metabolic rate in erythroderma (Inamadar, 2005 and Sam, 1978). No significant changes in arterial blood pressure was seen as body tends to maintain a normal level of arterial blood pressure through release of catecholamines (Roujeau, 19990).

FNAC of enlarged lymph nodes showed reactive hyperplasia except for one with paraneoplastic dermatomyositis wherein malignant cells were seen. In concordance to our study, previous studies have shown lymphadenopathy ranging from 21% to 33% of cases (Botella-Estrada, 1994; Kimgai, 2003 and Bandyaopadhyay, 1999). It regressed over a period of 4-6 weeks, as the erythrodermic state was treated except that associated with paraneoplastic erythroderma. Mucosal involvement in the form of erosions was present in cases with drug induced erythroderma. Palmoplantar affection was seen in erythroderma secondary to psoriasis, drug induced, eczema and paraneoplastic dermatomyositis. Ebonisation was most common nail change resulting from chronic itching. Scalp involvement is seen in form of plaques and scaling in cases of erythroderma secondary to psoriasis, generalised pustular psoriasis, pemphigus foliaceus and paraneoplastic dermatomyositis. Anaemia, leukocytosis, increased erythrocyte sedimentation rate are frequent findings. in erythroderma (Rothe, 2000; Abrahams, 1963 and Botella-Estrada, 1994). Eosinophilia was found in cases with DRESS (16.19%), drug induced erythroderma (9.1%) and photoallergic contact dermatitis (9.1%). Neutrophilia was present irrespective of sepsis or secondary infection. This can be attributed to transient neutrophilia seen in cases of infection, inflammation, acute stress and autoimmune conditions (Sam, 1978). However larger sample size study is needed to further elaborate this finding. The common cause of microcytic hypochromic anaemia is iron deficiency anaemia, and that of macrocytic is vitamin B12 and folic acid deficiency (Chrobák, 2001 and Massey, 1992). This occurs due to loss of iron through the shed skin and impaired absorption and utilization of iron and vitamin B12 (Sam, 1978). Serum aspartate transaminase and alanine transaminase were elevated in cases with aetiology secondary to DRESS syndrome and paraneoplastic dermatomyositis. Hepatitis is one of the known organ dysfunction known to occur during acute phase of DRESS syndrome (Berger, 2012). Hyperuricemia and hypocalcemia was seen in patients with erythroderma secondary to generalised pustular psoriasis and chronic plaque psoriasis (Qadim, 2013). In a study by Gisondi *et al* (Gisondi, 2014) prevalence of hyperuricemia was seen to be remarkably greater in psoriatic patients than in age-, sex-, and weight-matched control subjects, independent of coexisting metabolic disorders. Also, hypocalcemia contributes to development of generalised pustular psoriasis as well as aggravates pre-existing psoriasis.

Table 3 shows comparison of histopathology with other studies for histopathologic diagnosis. Histopathology correlated maximally with clinical diagnosis in erythroderma with paraneoplastic dermatomyositis, pemphigus foliaceus and generalised pustular psoriasis. Table 4 shows comparison of previous study with present study for aetiology of erythroderma. The most common aetiology found was erythroderma secondary to psoriasis vulgaris (35.48%). Its features may be present until the whole body develops exfoliative dermatitis (Sehgal, 2004). In two cases, generalized pustular psoriasis was the cause of erythroderma precipitated by liberal and widespread application of topical steroids. This was followed by erythroderma secondary to drug (n =7, 22.5%). There were four cases with aetiology of drug induced erythroderma and three cases with DRESS syndrome. The drugs implicated were loose medications, phenytoin and clindamycin. Clinically patient presented as itchy maculopapular rash spreading to involve trunk and extremities; resolving by scaling in 3-4 days. DRESS syndrome was seen secondary to rifampicin and phenytoin. It is a severe idiosyncratic drug reaction occuring 2 to 8 weeks after initiating the offending drug (Choudhary, 2013). The diagnosis of DRESS syndrome is based on the Japanese criteria (Table 5) (Choudhary, 2013). NBIE(6.45%) was diagnosed on basis of birth history of collodion membrane, winter aggravation and lamellar nature of scaling. Patients with pemphigus foliaceus (6.45%) presented with redness, scaling, erosions with positive Nikolsky sign and mousy odour. Paraneoplastic dermatomyositis(6.45%) had presentation of minimal scaling along with weakness in upper and lower extremity was present in 6.45% (n=2). Underlying associated malignancies were adenocarcinoma of breast and other was hepatocellular carcinoma. In paediatric erythroderma, psoriasis was found to be most common aetiology. This is contrast to study by Sarkar *et al* (Langford, 2000), where drug induced erythroderma was found to be most common. The sample size of paediatric population (n=4) study is small to comment on this difference.
Secondary infection in erythroderma occurs commonly due to superficial skin infection. These patients presented with fever, tenderness, delayed healing of erosions and leukocytosis with neutrophilia. Breach in skin barrier facilitates colonization and

systemic entry of commensals, exogenous and endogenous (gut flora) microorganisms. The incidence of septic complications is increased in the presence of altered body defence mechanisms (Inamadar, 2005). Upon culture of scales, trichosporon species was the most common species grown Trichosporon, an anamorphic fungi are isolated from soil, but occurs as normal commensal of humans. They are implicated in causing of superficial and invasive fungal infections in immunocompromised state (Colombo, 2011). The growth of pathogenic flora like MRSA, Staphylococcus aureus, Klebsiella pneumonia on from scales highlights the importance of maintaining strict asepsis while handling these patients. Electrolyte imbalance in form of hyponatremia and hyperkalemia was noted. The daily percutaneous water loss is high due to impaired barrier function of the skin resulting in increased transepidermal water loss (TEWL), and enhanced percutaneous fluid loss by transpiration (proportionate to the raised BMR) (Inamadar, 2005). Inadequate fluid replacement, manifests as dehydration and decreased urinary output. This is associated with electrolyte imbalance (low Na+ and high K+), and raised serum levels of urea and creatinine (prerenal uraemia) (Langford, 2000). Hypoproteinemia could be due to protein loss through scaling, chronic malnutrition, or dilution due to hypervolemia (Inamadar, 2005). Temperature dysregulation (22.5%) is presence of hyperthermia or hypothermia in absence of any secondary infection. Hyperthermia occurs due to increased basal metabolic rate, hypohidrosis (blockage of sweat duct in psoriasis), interleukin-1 (produced by damaged keratinocytes) (Luger, 1981) and raised environmental temperature (Inamadar, 2005 and Sam, 1978). Two patients with acute onset psoriatic erythroderma and sepsis had hypothermia along with chills at the time of presentation followed by hyperthermia. This alternate cycle of chills and fever is known to occur in erythroderma (Inamadar, 2005).

Limitations

The sample size taken is too small to comment on differences from other studies. The study duration was small. Also follow up was not included in study to know about relapse and long term sequel of the disease.

Conclusion

Erythroderma is an inflammatory disorder characterized by an extreme state of skin dysmetabolism. [30] It does not represent a defined entity, as it is the clinical presentation of a variety of diseases. Subtle clinical features of underlying diseases can still be present. Histopathology aids in diagnosis, however is not always confirmatory. Thus clinicopathologic correlation is essential in establishing diagnosis. Monitoring of vitals, fluid and electrolytes and biochemical abnormalities helps in early detection of complication thus aiding in its proper management.

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