Original Article

Causes and Features of Erythroderma

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Abstract

Introduction: Erythroderma is a generalised inflammatory reaction of the skin secondary to a variety of causes. This retrospective study aims to characterise the features of erythroderma and identify the associated causes of this condition in our population. Materials and Methods: We reviewed the clinical, laboratory, histological and other disease-specific investigations of 225 inpatients and outpatients with erythroderma over a 7.5-year period between January 2005 and June 2012. Results: The most common causative factors were underlying dermatoses (68.9%), idiopathic causes (14.2%), drug reactions (10.7%), and malignancies (4.0%). When drugs and underlying dermatoses were excluded, malignancy-associated cases constituted 19.6% of the cases. Fifty-five percent of malignancies were solid-organ malignancies, which is much higher than those previously reported (0.0% to 25%). Endogenous eczema was the most common dermatoses (69.0%), while traditional medications (20.8%) and anti-tuberculous medications (16.7%) were commonly implicated drugs. In patients with cutaneous T-cell lymphoma (CTCL), skin biopsy was suggestive or diagnostic in all cases. A total of 52.4% of patients with drug-related erythroderma had eosinophilia on skin biopsy. Electrolyte abnormalities and renal impairment were seen in 26.2% and 16.9% of patients respectively. Relapse rate at 1-year was 17.8%, with no associated mortality. Conclusion: Our study highlights the significant proportion of malignancy-related erythroderma in those whom common underlying causes such as dermatoses and drugs have been excluded. In cases of drug-related erythroderma, traditional medications and antituberculous medications are common causes in our population. Renal impairment and electrolyte abnormalities are commonly seen and should be monitored in patients with erythroderma.

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Introduction

Erythroderma is a dermatological reaction characterised by extensive erythema and scaling of the skin secondary to a variety of causes. An improved understanding of the characteristics and aetiologies of this condition will guide management. In this retrospective study, we aim to describe the characteristics and explore the associated causes of the condition in our population.

Materials and Methods

The profile of all inpatients and outpatients with erythroderma who visited the National Skin Centre (NSC), during a 7.5-year period from 1 January 2005 through 30 June 2012 was retrospectively analysed. Erythroderma was defined clinically as erythema and scaling involving more than 90% of the body surface. The data collected included patient demographics, drug history, past medical and dermatological history, clinical findings (skin erythema, scaling, mucosal or nail involvement, lymphadenopathy, organomegaly, pedal oedema, pruritus, fever or chills), laboratory investigations (haematologic parameters, serum electrolytes, liver and renal function, albumin and inflammatory markers), skin biopsies, cultures and other disease-specific investigations (such as imaging and bone marrow examination). The disease course was analysed, with a follow-up period of 0 to 7.5 years.

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Results

There were 225 patients diagnosed with erythroderma during the study period. The mean age of the patients was 66.0 years (range, 1 month to 95 years), median 70 years, with a male-to-female ratio of 3:1. Majority were Chinese (78.0%), followed by Malays (15.0%), Indians (3.5%) and other ethnic groups (3.5%).

The most common clinical presentations were generalised erythema (100.0%), scaling (92.4%) and pruritus (92.0%). Lymphadenopathy (32.9%), chills (24.0%) and pedal oedema (19.6%) were common, while fever (4%), nail (3.5%), mucosal involvement (2.0%) and organomegaly (1.0%) were uncommon (Table 1).

Eosinophilia (58.2%), hypoalbuminemia (45.3%), electrolyte abnormalities (26.2%) and renal impairment (16.9%) were common laboratory findings. Skin or wound cultures were done in 24.4% of the patients, in whom 92.7% (51/55) had positive cultures results, with methicillin-sensitive *Staphylococcus aureus* (MRSA) being the most frequent organism isolated (64.7%, 33/51). In patients with positive skin or wound cultures, 17.6% (9/51) had associated raised inflammatory markers (total white cell count and C-reactive protein (CRP)), 35.3% (18/51) had thermodysregulation (fever or chills) and 5.9% (3/51) had bacteraemia. Bacteraemia occurred in 15.9% (7/44) of those tested.

Serum tumour markers were measured as part of the malignancy workup in 60.0% (135/225) of the patients. These included alpha-fetoprotein (AFP), carcinoembryonic agent (CA), prostate-specific antigen (PSA) (in males), CA 19-9 and CA 125 (in females). At least 1 of these markers were abnormal in 35.6% of these patients (48/135). However, there was no associated malignancy when further investigated in these cases, except for 1 patient with raised AFP and underlying haepatocellular carcinoma (HCC).

Skin biopsy was performed in 76.0% of the patients. The most common histological findings were subacute or chronic dermatitis (35.1%), followed by psoriasiform dermatitis (29.3%). In the biopsy specimens of patients with drug-related erythroderma, 52.4% had findings of eosinophilia, 4.8% showed interface dermatitis, and 4.8% had both of these features. In all the 4 patients with cutaneous malignancies, histological analysis was suggestive or diagnostic of cutaneous T-cell lymphoma (CTCL).

The aetiology of erythroderma can be classified into 4 main categories (Table 2). The most common causative factors were pre-existing dermatoses (68.9%, 155/255), idiopathic causes (14.2%, 32/225), drug reactions (10.7%, 24/225), and malignancies (4.0%, 9/225). Among the pre-existing dermatoses, endogenous eczema was most common (69%, 107/155), followed by psoriasis (20.6%, 32/155). The most commonly implicated drugs were traditional medications (20.8%, 5/24) and antituberculous medications (16.7%, 4/24). Other implicated agents include penicillin, omeprazole, Keppra®, thiazides, calcium channel blockers and Irressa®.

Forty-five percent (4/9) of the malignancies were primary cutaneous malignancies, consisting of mycosis fungoidis (3/4) and Sezary syndrome (1/4), while 55.0% (5/9) were solid-organ malignancies, with 2 cases of haepatocellular carcinoma, 1 case each of nasopharyngeal, colorectal and non-small cell lung carcinoma. Four out of 5 cases of solid-organ malignancies were diagnosed after the onset of erythroderma as part of the malignancy evaluation, while 1 patient had pre-existing HCC. The initial findings of colorectal, lung and HCC were seen on computed tomographic scans, while nasopharyngeal carcinoma (NPC) was seen on nasoendoscopy.

In the treatment of erythroderma, 48.9% of the patients received antibiotics, 42.2% received systemic steroids and

Table 1. Clinical Features of Erythroderma

Clinical Feature	Wong KS et al, 1988[6] (%)	Pal and Haroon, 1998[1] (%)	Akhyani et al, 2005[5] (%)	Li J et al, 2012[9] (%)	Present Study (% Out of 225 Patients)
Erythema	100.0	100.0	100.0	100.0	100.0
Scaling	100.0	84.4	100.0	100.0	92.4
Pruritus	NA	86.0	97.5	87.7	92.0
Lymphadenopathy	22.0	55.5	21.3	19.2	32.9
Chills	NA	64.4	NA	31.1	24.0
Pedal oedema	44.0	44.4	14.4	37.7	19.6
Fever	12.0	40.0	33.6	40.0	4.0
Nail involvement	NA	80.0	NA	29.6	3.5
Mucosal involvement	NA	36.6	1.0	NA	2.0
Organomegaly	9.0	25.5	4.0	NA	1.0

NA: Not available

8.4% required other types of systemic agents, including dapsone, ciclosporin, methotrexate (MTX), azathioprine, acitretin and interferon-alpha (used in Sezary syndrome). The outcomes of the patients were fairly good with no deaths directly related to the condition. Relapse rate at 1-year was 17.8%, most commonly in patients with underlying endogenous eczema.

Discussion

In our study, patients presented at an older age, with mean age of onset at 66.0 years. This is older than figures quoted in other studies, which ranged from 41.6 to 61.0 years.[1-4] There were 3 times more males in our study, in concordance with other studies.[1,2,5-7]

The prevalence of most clinical features, including erythema, scaling, pruritus, lymphadenopathy, oedema, chills, organomegaly and mucosal and nail involvement, were similar to other studies.[1,5] However, the prevalence of fever (4.0%) among our patients was much lower compared to other studies (33.0% to 37.8%).[3,5,8]

Table 2. Aetiologies of Erythroderma

Cause	Percentage (%) Out of 225 Patients
Underlying dermatoses	68.9
Endogenous eczema	47.6
Psoriasis	14.2
Others*	7.1
Idiopathic	14.2
Drugs	10.7
Malignancy	4.0
Cutaneous	1.8
Solid organ†	2.2
Others‡	2.2

*Includes acquired icthyosis, chronic actinic dermatoses, pityriasis rubra pilaris, seborrhoeic dermatitis, bullous pemphigoid, pemphigus foliaceous and actinic keratosis.
†Includes 2 cases of hepatocellular carcinoma and 1 case of colorectal carcinoma, nasopharyngeal carcinoma and non-small cell lung carcinoma each.
‡Includes contact dermatitis, papuloerythroderma of Ofuji and erythema toxicum neonatorum.

Laboratory investigations showed renal impairment in 16.9% of our patients, likely secondary to dehydration from fluid losses and poor oral intake during severe acute illness. In contrast, although King et al[8] and Yuan et al[3] reported multiple other laboratory abnormalities, renal impairment was not reported. Skin or wound cultures were positive in 92.7% of the patients tested; however, only 17.6% of these patients had associated raised inflammatory markers and 5.9% associated bacteremia. Hence, the routine use of systemic antibiotics in patients with positive skin or wound cultures is not recommended, as these may represent skin commensals.

In patients with pre-existing dermatoses that is poorly controlled, erythroderma may occur during a flare of the skin disease.[1,3,5,9] In such cases, the diagnosis is usually obvious. Otherwise, erythroderma remains a diagnostic challenge which often entails a thorough drug history and malignancy screening. In the latter, there is no consensus of when to initiate and what investigations to conduct. In a significant number of cases, despite extensive investigations, no cause was found and these were designated to have an idiopathic aetiology.

The various categorical causes of erythroderma in our study appear similar in frequency compared to previous studies (Table 3). Although malignancies were the cause of erythroderma in only 4.0% of our patients, from a practical point of view, they constituted 19.6% of the cases when drugs and underlying dermatoses were excluded. As such, an active search for an associated malignancy should be carried out in such cases. The frequency of malignancies in our study population was comparable to other studies (1.0% to 11.3%),[3,5,9,10] comprising of both solid-organ and cutaneous malignancies. The higher incidence of HCC associated with erythroderma might be accounted for by the prevalence of this cancer in Asia, largely due to the ubiquity of hepatitis B infection in this part of the world.[11]

In patients diagnosed with malignancy in our series, all had normal levels of serum tumour markers except for 1 patient with HCC. On the other hand, the tumour markers were abnormal in 35.6% of the patients in whom the levels were measured, and 99.3% of them did not have an underlying

Table 3. Categorical Aetiologies of Erythroderma in Previous Publications and the Present Study

Aetiologies	Relative Incidence (%)					
	Wong KS et al 1988[6]	Pal and Haroon 1998[1]	Akhyani et al 2005[5]	Yuan XY et al 2010[3]	Li J et al 2012[9]	Present Study 2012
Underlying dermatoses	57.0	74.4	57.9	72.0	70.8	68.9
Drug reactions	13.0	5.5	21.6	17.0	12.7	10.7
Malignancies	0.0	5.5	11.3	4.9	2.3	4.0
Idiopathic	29.0	14.6	7.2	6.1	14.2	14.2

malignancy. Hence tumour markers are not useful as a screening tool for malignancy. The workup in such patients should instead rely on imaging and endoscopies, guided by clinical findings. Features previously noted to be suggestive of an underlying malignancy include combinations of presence of systemic symptoms, an insidious onset, lack of a pre-existing dermatosis and resistance to standard treatment.[12]

In drug-induced erythroderma, skin biopsies revealed eosinophilia in 52.4% of our patients compared to 16.6% in the study by King et al.[8] Skin biopsy was also effective in the diagnosis of primary cutaneous malignancies in all 4 of our patients, with 3 or fewer biopsies required per patient for the diagnosis to be made.

In the literature, common drugs implicated in erythroderma include antiepileptics (such as phenobarbitone, carbamazepine, and phenytoin), antibiotics (such as penicillin, sulphonamides and antituberculous drugs), gold, lithium salts and allopurinol.[4,5,12,13] The major causative drugs vary between studies, and appear to correlate with regional endemic diseases and cultural norms.[3,9] In our study, antituberculosis medications including isoniazid and rifampicin, as well as traditional Chinese medicine were the most common causative drugs. This may be due to the higher prevalence of tuberculosis in Southeast Asia, and the relatively widespread use of traditional Chinese medicine in Singapore.

In contrast to some earlier studies that have quoted high mortality rates mainly attributed to drugs or lymphoma (11.0% to 64.0%),[8,14-16] there was no mortality arising directly from erythroderma in our study population. Some other studies had also quoted low mortality rates in the range of 0.0% to 2.0%.[5,9,17]

Conclusion

Erythroderma is commonly caused by pre-existing dermatoses and drugs. A thorough drug history should be taken including traditional medications and supplements, and if present, eosinophilia seen on skin biopsy supports a drug aetiology. However, when these have been excluded, an associated malignancy is present in a significant proportion of cases and should be actively screened for. With similar frequencies of both cutaneous and solid organ malignancies, malignancy screen should include both cutaneous and solid organ malignancies. Renal impairment and electrolyte abnormalities are commonly seen and should be monitored in patients with erythroderma.

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