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Erythroderma: A clinical-etiological study of 82 cases

Erythroderma is an uncommon skin disorder characterized by generalized reddening and scaling of over 90% of the skin. It represents a maximal stage of skin irritation induced by several skin diseases such as psoriasis, contact dermatitis, drug reactions, and mycosis fungoides. Data including the clinical symptoms, laboratory examinations and skin biopsies were collected from 82 erythroderma patients admitted to our hospital in the period between Jan.1st, 2003 and Dec.31st, 2008. According to clinical findings, laboratory findings and biopsy results, the most common causative factors were pre-existing dermatoses (72.0%), followed by drug reactions (17.0%), idiopathic causes (6.1%) and malignancies (4.9%). Among the pre-existing dermatoses, psoriasis is the most common etiology (30.5%). We also found hyper-eosinophilic syndrome, sarcoidosis and dermatomyositis could be causes of erythroderma. In the drug-induced group, Chinese traditional herbal medicines were probably the most frequently implicated drugs in our series, with 9 of the 14 cases (64.3%). Follow-up information was obtained for 65 patients, and most of our patients had improved symptoms after treatment. In our series we found a high percentage of erythroderma secondary to pre-existing dermatoses and a low percentage of erythroderma secondary to malignancy. Among drugs as an etiological group, Chinese traditional herbal medicines were the most frequent drugs. From our follow-up study, the prognosis of most patients with erythroderma is relatively good.

Key words: erythroderma, etiological cause, clinical symptoms, laboratory examinations, skin biopsies, Chinese traditional herbal medicines

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Erythroderma or generalized exfoliative dermatitis is a striking but uncommon clinical entity in the practice of most dermatologists. Erythema and scaling occur as a generalized inflammation involving more than 90% of the body surface. Erythroderma may happen at any age, varying from the neonatal period to ninety years old. It is considered as a generalized spread of a dermatosis such as psoriasis, drug eruption etc. We collected data from 82 erythroderma patients admitted to our hospital in the period between 2003 and 2008. Our study aimed to examine the causes of erythroderma in our community, providing important clinical insight into the causes and prevention of erythroderma.

Patients and materials

The patient profiles composed of all patients of both genders and any age diagnosed with erythroderma by the dermatology department, Air Force General Hospital, during the period from Jan.1st, 2003 to Dec.31st, 2008. Our department is one of the largest dermatology clinics in

Beijing and often receives patients from distant areas of mainland China. There are approximate 400,000 visits per year.

All the patients diagnosed with erythroderma had developed erythema involving more than 90% of the body surface, as calculated by Wallace's rule of nine. A detailed history was recorded and a thorough examination was performed for each patient. The history included personal data, the onset and evolution of the erythroderma, duration and symptoms, aggravating factors, previous skin diseases or drug intake history. Then, a thorough examination was performed and special attention was given to assessment of the skin, lymphnodes, temperature, edema and so on. Laboratory examinations included blood cell count, erythrocyte sedimentation rate (ESR), elevated C reaction protein and serum albumin, electrolytes, blood sugar, liver and kidney functions, urine and stool examination, and chest X-ray, abdominal ultrasound and electrocardiogram (ECG). If necessary, any other diagnostic investigations, such as serum creatase, bone marrow aspiration and electromyogram (EMG) were performed. Sometimes additional skin studies such as patch tests, photosensitivity tests or photo patch tests were also performed. Clinical and laboratory data were collected for

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every patient's case record sheets from the primary and secondary visits to the dermatology department. All data were recorded and analyzed.

Results

Epidemiology/Demographics

In the six year study period, 82 patients diagnosed with erythroderma were admitted to our hospital. There were about 2,400,000 patient visits to our department in total during this period. The mean age of onset was 53.4 years, with the youngest patient one-month-old and the oldest patient 82 years old. Detailed information about the age range of patients is summarized in *table 1*. Most people presenting with erythroderma in our study were between 60-70 years old. The highest incidence of erythroderma was found in the age group sixty-one to seventy years old (28.1%). The majority of patients (18.3% + 23.2% + 28.1% + 11.0% + 1.2% = 81.8%) were above forty years old. The male (n = 67): female (n = 15) ratio was 4.7: 1. All the patients in this study were from mainland China, except one girl with atopic dermatitis from Hong Kong, China. Twenty patients (24.4%) developed acute erythroderma within hours to 3 days. The disease duration varied from 24 hours (drug-induced erythroderma) to 14 years (congenital ichthyosiform erythroderma). The mean duration was 4.1 month.

Clinical findings

Itching, the most common complaint, was recorded in 79 patients (93.9%). Thirty two patients (37.8%) had a fever (temperature equal to 38 °C or higher) during the episode and lymphadenopathy was found in 20 (15.9%) patients. Constipation was found in 10 (12.2%) patients. All the patients had generalized erythema involving more than 90% of their body surface and various degrees of scaling. Edema, nail changes, hepatomegaly and splenomegaly were also reported in 21 (25.6%), 30(36.6%) and 3 (3.6%) patients respectively. Clinical symptoms and the incidence of each symptom can be seen in *table 2*.

Laboratory findings

Laboratory abnormalities were also detected, including elevated ESR (63.4%), increased WBC count (54.9%), higher level of C reaction protein (75.6%), hypoproteine-

Table 1. Age distribution of patients with erythroderma

Patient's age (years old)	Number	Percentage (%)
0-10	2	2.4
11-20	6	7.3
21-30	2	2.4
31-40	5	6.1
41-50	15	18.3
51-60	19	23.2
61-70	23	28.1
71-80	9	11.0
81-90	1	1.2
Total	82	100

Table 2. Clinical findings in the present series of patients with erythroderma

Clinical findings	Number	Percentage (%)
Itching	79	93.9
Temperature elevation (≥ 38 °C)	31	37.8
Chills	15	18.3
Constipation	10	12.2
Erythema	82	100
Scaling	82	100
Nails change	30	36.6
Lymphadenopathy	13	15.9
Edema	21	25.6
Hepatomegaly and splenomegaly	3	3.6

mia (13.4%) and eosinophilia (over 400 cells/ μ L, incidence rate was 20.7%). We also found higher levels of serum muscle enzymes in one patient and EMG showed a change in dermatomyositis. Seven patients were suspected of having hypereosinophilic syndrome. After bone marrows were isolated and examined, only three bone marrow specimens out of seven showed specific manifestations of hypereosinophilic syndrome.

Biopsy, histopathology and clinical correlations

Skin biopsies were taken in 42 cases (51.2%). The biopsies were often performed within the first three days after the patients were admitted to hospital. Skin biopsy was not performed for the rest of the patients because the causes of erythroderma were very clear for them, such as previously known dermatoses (in the follow-up examinations of the patients after the erythroderma subsided the original dermatoses became recognizable again) or a drug history before the appearance of erythroderma (as the onset of erythroderma due to drugs was usually acute and the color of the skin lesion usually was ruby-red. The patient was cured or significantly improved after the removal of the drugs involved). Biopsies were taken from more than one location in 2 cases of granuloma fungoides (MF), 1 case of Sezary syndrome and five cases of undetermined cause. Biopsies of lymph nodes were taken in four cases as these four patients were without a history of dermatological disease, or without typical itching, showed painless swollen lymph nodes and were suspected clinically to suffer from skin tumors. Only one of them suggested Sezary syndrome, one revealed changes of sarcoidosis, the other two showed dermatopathological lymphadenopathy. Biopsies for both skin and muscle were taken in one case of dermatomyositis. Biopsies and histopathology helped us to reach a diagnosis of some underlying causes, especially psoriasis, MF, Sezary syndrome, sarcoidosis and hypereosinophilic syndrome.

Etiology

Etiologically, the patients were categorized into four groups according to the clinical, laboratory and histological findings in each individual patient: pre-existing dermatoses (72.0%, *table 2*), drug reactions (17.0%), malignancies (4.9%) and undetermined etiology (6.1%). The most common cause was psoriasis (n = 25). Dermatitis comprises atopic dermatitis (n = 3), contact dermatitis (n = 6), airborne

dermatitis (n = 4), seborrheic dermatitis (n = 4), photoallergic dermatitis due to wild celery (n = 1). Contact dermatitis due to paraphenylenediamine of hair dye was reported in 5 cases, perfume to cover the smell of bromhidrosis in one case. There were ten patients with pityriasis rubra pilaris. The type of ichthyosis was non-bullous ichthyosis. In the pre-existing group, we also found that hypereosinophilic syndrome, sarcoidosis and dermatomyositis could also be causes of erythroderma, which was very rare in previous studies but has been seen in some case reports.

In the drug-induced group (n = 14), one patient had erythroderma due to penicillin, one patient due to amoxicillin, one patient due to sulfanilamide and another two due to indomethacin. For the other nine cases, erythroderma was probably induced by oral or topical use of traditional Chinese herbal medicines. We confirmed that some traditional medicines might be the triggers through patch tests after the erythroderma had cleared. We found patch tests using each single traditional herbal medicine in the combined prescriptions separately were negative for allergens, except for two cases. One was positive to *Boswellia carterii* and *Commiphora myrrha*, the other was to *Colla Apis*. However, patch tests using all the combined prescriptions as allergens were positive or strongly positive. We did not use oral provoking tests because of the potentially serious consequences due to drug reactions. All Chinese traditional herbal medicines that might cause erythroderma are listed in table 4. Among these traditional medicines, Shuanghuanglian Koufuye and Qingkailin Zhusheyeye are used orally or intravenously as antipyretic analgesics. Angelicae Pubescentis and Loranthis Decoction, Qizheng Xiaotong Tie, SheXiang Zhitong Gao and *Colla Apis* are always used as oral or external medications to treat arthralgia, while Complex Garter Snake Decoction was used to treat trigeminal neuralgia. Another two cases were due to uncertain complex decoction prescriptions, which were used to treat bromhidrosis and depilation. Concerning the correlation of malignancies to erythroderma, one patient had gastric cancer with brain metastasis, two had MF (Mycosis Fungoides), the other had Sezary syndrome. These were all confirmed by biopsy results. No cause could be found in 5 patients, although thorough investigations and skin biopsies on more than one spot were taken.

Prognosis

Follow-up information was obtained for 65 patients, the other patients could not be reached. As shown in table 5,

Table 3. Diagnostic split-up in 59 patients with pre-existing dermatoses as a causative factor of erythroderma

Pre-existing dermatoses	Number	Percentage (%)
Psoriasis	25	30.5
Dermatitis	18	22.0
Pityriasis rubra pilaris	10	12.2
Congenital ichthyosiform erythroderma	1	1.2
Hypereosinophilic syndrome	3	3.7
Sarcoidosis	1	1.2
Dermatomyositis	1	1.2
Total	59	72.0

most of our patients had improved symptoms after treatment, but only one third of them were cured. Two patients with erythroderma died: one was due to gastric cancer with brain metastasis, the other was due to hypereosinophilic syndrome because of cardiac failure. Most of our patients showed a good prognosis and they are still in our follow-up study.

Discussion

Erythroderma is not a very common disease clinically, but it can often be urgent and life-threatening [1]. So if dermatologists aim to treat or cure patients with erythroderma, it is very important to understand its etiology in each patient. But sometimes the causes of erythroderma remain a challenge to doctors. The clinical features are non-specific and symptoms such as edema, scaling, nails

Table 4. Chinese traditional herbal medicines as etiology of erythroderma

Chinese traditional herbal medicines	Number	Patch Test
Shuanghuanglian Koufuye	1	++
<i>Lonicera japonica</i> Thunb		-
<i>Ranunculaceae</i>		-
<i>Forsythia suspensa</i>		-
Qingkailin Zhusheyeye	1	++
<i>Gardenia jasminoides</i> Ellis		-
<i>Cornu Bubali</i>		-
<i>Radix Isatidis</i>		-
<i>Radix Scutellariae</i>		-
Angelicae Pubescentis and Loranthis Decoction	1	+++
<i>Heracleum hemsleyanum</i> Diels		+
<i>Ramulus Taxilli</i>		-
<i>Asarum sieboldii</i> Miq. <i>Veratrum baillonii</i> Franch		-
Qizheng Xiaotong Tie (external medication)	1	++
<i>Lamiophlomis rotata</i>		-
<i>Rhizoma Curcumae Longae</i>		-
<i>Zanthoxylum bungeanum</i> Maxim		+
<i>Cornu Bubali</i>		-
SheXiang Zhitong Gao (external medication)	1	+++
<i>Moschus</i>		+
<i>Boswellia carterii</i>		++
<i>Commiphora myrrha</i>		++
<i>Cinnamomum cassia</i> Presl		-
<i>Colla Apis</i> (external medication)	1	++
Scorpio and Centipede in combined Garter Snake Decoction	1	+++
<i>Scorpio</i>		+
<i>Scolopendra</i>		+
<i>Bombyx Batryticatus</i>		-
<i>Saposhnikovia divaricata</i>		-
<i>Periostracum Cicadae</i>		-
Uncertain Combined decoction prescriptions to treat pruritic diseases	1	++
	1	++

Table 5. Prognosis of 65 patients by telephone follow-up in July, 2009

Etiology	Cleared	Improved	Unchanged	Dead
Pre-existing dermatoses (n = 46)	10	35	2	1
Psoriasis (n = 22)	6	16	0	0
Dermatitis (15)	3	15	0	0
Pityriasis rubra pilaris (n = 8)	0	8	2	0
Hypereosinophilic syndrome (n = 1)	0	0	0	0
Drug reactions (n = 10)	10	0	0	0
Malignancy (n = 4)	2	1	0	1
Undetermined (n = 5)	0	3	2	0

changes or itching may not be traced to any specific cause. Only by thorough investigation of the clinical, laboratory and histological findings, as well as history of each individual patient, can one make a diagnosis of erythroderma. According to Sigurdsson and colleagues' study [2], the annual incidence of erythroderma is 0.9 patients per 100,000 inhabitants. But they did not give the annual erythroderma incidence in patients with skin diseases. In our study, the annual incidence of erythroderma in patients with skin diseases was 0.003% (82 in 6 years in 400,000/year). Because patients admitted to our department came from all over our country, we could not calculate the incidence of erythroderma among local inhabitants. In our series the mean age of onset was 53.4 years and most of patients with erythroderma were above forty years (81.8%). Men outnumbered women. Such findings are in accordance with many other studies [3, 4], but in our study the number of male patients was 67, much higher than the number of females (n = 15). It may be that men in China face more stress, work with toxic substances, touch other medications and have different environmental circumstances etc.

The highest incidence of erythroderma was the group aged sixty-one to seventy (28.1%). The majority of patients with erythroderma in our study were above forty years (81.8%). Previously, Botella-Estrada *et al.* [5] also reported similar findings. Similar to other reports [3, 6], itching, erythema and scaling were found to be the most common complaints among our patients. But we found a higher percentage of fever, elevated WBC count and a lower percentage of lymphadenopathy, hepatomegaly and splenomegaly, elevated ESR and eosinophilia, in comparison with the Hasan and Jansen series [3]. We also found some other clinical and laboratory data such as chills (18.3%), constipation (15.9%) and hypoproteinemia (13.4%), which have rarely been mentioned before. Skin biopsies, helpful in more than half of the cases in which they were performed in our series and always regarded as a useful investigation, are recommended to be carried out as soon as possible. Sometimes they should be repeated in a different area and a different stage of erythroderma for a final diagnosis [4, 7].

Our study had a relatively high percentage (72.0%) of erythroderma secondary to pre-existing dermatoses, in accordance with earlier reports on erythroderma (25% and 30%, respectively) [8, 9], but a similar percentage to the report by Sabrina Pal *et al.* (74.4%) [4]. In our series, psoriasis was the most common underlying etiology of pre-existing dermatoses. This was also consistent with report from Sabrina Pal *et al.* [4]. Pityriasis rubra pilaris

is uncommonly reported as a cause of erythroderma in other studies [3-5, 9]. Maryam Akhyani *et al.* reported pityriasis rubra pilaris as a causative factor of erythroderma in 8.2% of their patients [10]. In our study the percentage of pityriasis rubra pilaris was higher (12.2%) than most of previous reports. As a result, we concluded that there might be a higher frequency of pityriasis rubra pilaris or a greater tendency for its generalization in our district. Congenital ichthyosiform erythroderma is a very rare condition in our study, as in previous reports. In our series we also found sarcoidosis (n = 1), dermatomyositis (n = 1), hypereosinophilic syndrome (n = 3) as the causes of erythroderma, which have never or rarely been mentioned in previous reports. Sarcoidosis and dermatomyositis were shown as a causative factor of erythroderma, which is very rare. Sarcoidosis is a systemic disease that can involve almost all organ systems and is characterised by non-caseating granuloma infiltrations. Cutaneous manifestations occur in 25% of patients with systemic sarcoidosis. The most common are papular, nodular, plaque lesions and involvement of scars. Rare cutaneous expressions of sarcoidosis include erythroderma [11]. Erythroderma linked to dermatomyositis is also a very unusual event and a few cases have been reported in the literature [12-14]. Although the incidence is very low, we did not find other causes for erythroderma in these patients. Further studies will need to confirm this correlation.

In our study, we found a similar percentage of drug-induced cases to previous reports [3-5, 10, 15]. The skin lesions appeared 2-3 days after oral administration of Chinese herbs, then quickly spread to the whole body. Erythroderma was observed one day after topical use of *Colla Apis*, accompanied by oral *Colla Apis* herb supplement. The skin lesions in other patients were observed one week after topical use of other Chinese herb medicines, these patients were improved after the removal of the drugs involved. However, erythroderma was observed 1-4 days after topical use of the same Chinese herb medicines again. They were all improved after the removal of the drug involved. Unfortunately, we were not able to perform the patch test to standard allergens. Amoxicillin is often the major cause for drug eruptions in mainland China, but in our study we found only one case. Chinese traditional herbal medicines were the most frequently used drugs in our series, with 9 of the 14 cases (64.3%). In the case of oral traditional herbal medicines, all 4 patients showed positive patch tests. One reason might be that these patients have previously used these herb medicines topically, then systemic contact dermatitis is observed after oral administration of the same Chinese herb medi-

cines again, as reported by Torres *et al.* [16]. Many western drugs, including indomethacin, which are often used to cure or relieve pain, could be a cause for drug eruption. In our study, we found many Chinese traditional herbal medicines used to treat analgesia can also be the etiology of drug eruptions. Maybe there are similar chemical components in these herbal medicines as in those western analgesic drugs. This phenomenon is very interesting. Could our ancestors of thousands of years ago have imagined that some active chemical component in some herbal medicines could cure or relieve pain without modern instruments? There are many complicated chemical components in each Chinese traditional medicine, so we are not sure which chemical component was the real ring-leader up to now. Now in clinical practice we find more and more drug eruptions due to Chinese traditional herbal medicines have occurred because many Chinese people think that Chinese traditional herbal medicines have very few adverse effects and prefer to choose them as first-line therapies. This study reminds us that we should pay particular attention to traditional Chinese herbal medicines. Pharmacokinetics and mechanisms of these herbal drugs are very complicated and still not very clear, let alone the interactions between each herbal medicine in a combined prescription. This may be the reason why some patients show negative results to each ingredient when using patch tests, while they have positive responses to complex prescriptions. However, we are not very sure that in this study all the herbal medicines used in China that may cause erythroderma have been identified, as we did not perform patch tests in normal controls. The patch test positive herb medicines such as *Boswellia carterii*, *Commiphora myrrha* and *Colla Apis* have also been reported by other researches [17-20].

MF and Sezary Syndrome were the most frequent malignant causes of erythroderma, but occasionally erythroderma was associated with internal malignancies. So, for patients with a previous history of known dermatoses whose clinicopathological features are inconclusive, we should investigate carefully to rule out any underlying malignant causes. In our series, after thorough examination, we found one patient with erythroderma had gastric cancer with brain metastasis. The percentage of malignancies as a cause for erythroderma is still relatively low in our study and previous reports [8, 9]. The pathological reason for erythroderma for five patients remained elusive. This group is also called idiopathic erythroderma or red man syndrome [21], but we prefer the name undetermined erythroderma, because the etiology will be identified in time. Some authors think these patients may represent a pre-malignant phase [4]. So a close follow-up might allow doctors to identify the causes and start earlier treatment. We obtained follow-up information from 65 patients. Other patients were unavailable to be contacted by telephone. Up to now we found only two patients with erythroderma were dead, one due to gastric cancer with brain metastasis, the other due to hypereosinophilic syndrome,

because of cardiac failure. Most of our patients were cured or improved. Our series was in accordance with previous reports [3, 10]. Our studies would therefore support the perception [4, 10] that erythroderma, although often bringing distress to patients, and sometimes even life-threatening, is associated with a relatively good prognosis in most cases. ■

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