

## Erythroderma: analysis of 247 cases

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The profile of 247 patients with erythroderma during a 23 year period from January, 1962 through March, 1985, with a follow-up period ranging from 1 to 26 years were analysed. The patients presented with diffuse erythema, scaling and pruritus of more than 2 months' duration, and the age ranged from 16 to 60 years. Psoriasis was the most frequent underlying disease with an estimated frequency of 44.9%, the reaction to the use of drugs appeared in 7.3% of total cases and association with reticulosis showed a frequency of 4.1%. The cause of the erythroderma could not be determined in 29.2% of the cases. Sex differences in terms of underlying diseases were not observed. One or more skin biopsies along with the clinical findings were diagnostic or suggestive of the underlying disease in 63.6% of the cases. Repeated skin biopsies are recommended as the best method for etiologic diagnosis of erythroderma. At  $P=0.05$  significance level, masculine/feminine ratio of 2 : 1 was found. The question arises whether causal agent of erythroderma may not be somehow related to different exposure by sex to environmental antigens.

*Dermatitis, exfoliative; epidemiology incidence.*

### Introduction

Erythroderma is a syndrome characterized by diffuse erythema, scaling, pruritus and prolonged course. Systemic manifestations may be present and prognosis is cause-dependent (Abrahams et al<sup>1</sup>; Adam<sup>2</sup>; Fitzpatrick et al<sup>3</sup>; Gatti et al<sup>4</sup>; Helm<sup>10</sup>; Nebenzahl et al<sup>13</sup>; Nicolis & Helwig<sup>14</sup>; Nigam et al<sup>15</sup>; Rook et al<sup>17</sup> and Sampaio et al<sup>18</sup>).

In 1868, Hebra (apud Abrahams et al<sup>1</sup> and Nebenzahl et al<sup>13</sup>) proposed a classification based on clinical features: Hebra's pityriasis rubra, Brock's exfoliative dermatitis, scarlatiniform erythema and epidermal exfoliative dermatitis.

In 1913, Nicolis and Helwig<sup>14</sup>, after studying 135 patients with erythroderma, proposed a classification based on etiology: a) use of drug related - 40%; b) previous dermatosis related - 26.8%; c) mycosis fungoides and lymphoma related - 17.8%; d) internal malignancy - 2.8%; e) miscellaneous etiology - 0.7%; and f) unknown etiology - 11.9%.

Montgomery<sup>12</sup> established another classification based on histopathologic findings: a) idio-

pathic or primary; and b) secondary to an underlying dermatosis or reticulosis.

According to Rabello et al.<sup>16</sup>, the patients with erythroderma do not show any significant alteration of routine laboratory tests. Montgomery<sup>12</sup> stressed usefulness of multiple skin biopsies as a diagnostic and follow-up method.

Treatment must be directed towards the underlying diseases, although general measures should not be forgotten (Nebenzahl et al)<sup>13</sup>.

The objective of the present work is to profile the etiology of erythroderma and to verify if there was a predominance of the syndrome according to sex.

### Subjects and methods

Two hundred and forty seven patients with erythroderma seen at Dermatology Unit of a Hospital of Clinics located at the city of S. Paulo, Brazil, from 1962 through 1985, were studied. Diffuse erythema and scaling accompanied by pruritus

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lasting over two months in duration were used as diagnostic criteria. The patient's age and place of origin registered at the first visit were used for statistical analysis.

The patients were grouped according to the clinical diagnosis as seen:

- a) Related to previous dermatosis: psoriasis, eczema, atopic eczema, seborrheic eczema, lamellar ichthyosis, erythrokeratoderma (systemic and progressive forms), pityriasis rubra pilaris and Darier's disease;
- b) Drug use related: contact eczema, systemic eruption by drug use and photosensitivity;
- c) Reticulosis and leukemia related: lymphoma, mycosis fungoides and Sézary's syndrome;
- d) Miscellaneous: nodular scabies;
- f) Unknown etiology: the patients who did not have a known cause at the last visit.

Light microscopy study of skin biopsies was done and showed one of the following patterns:

- a) Subacute or chronic dermatitis;
- b) Subacute or chronic psoriasiform dermatitis;
- c) Psoriasis;
- d) Vasculitis;
- e) Suggestive of lymphoma;
- f) Others: lamellar ichthyosis, epidermolytic hyperkeratosis and Darier's disease, and
- g) Dermatopathic lymphadenitis.

The study has been designed as a case study\* (Forattini<sup>5</sup> and Leser et al).<sup>11</sup> The subject group was compared to patients with dermatosis without-erythroderma from the same hospital during the same time period.

The Special Program for Social Science (SPSS) was used for the analysis of the data.

In order to compare the ratio between three or more categories in the contingency tables, Goodman's<sup>8</sup> or Kolmogorov-Smirnoff's (apud Costa-Neto)<sup>3</sup> tests, along with Pearson's chi-square statistics (Costa-Neto)<sup>3</sup> were applied, respecting the frequency restrictions.

As for the tendency evaluation, adjustment by the method of minimum square and the regression line was adopted, and the angular coefficient test was applied, according to Student's t distribution, with the necessary adjustments. The comparison

between two angular coefficients, with the same adjustment, was possible due to Student's t distribution (Costa-Neto)<sup>3</sup>. The significance level adopted was P=0.05.

## Results

Table 1 shows a greater number of feminine patients in the group without erythroderma ( $t_{calc}=5.051$ ; c.p. (cut point)=2.131), and a greater number of masculine patients in the group with erythroderma ( $t_{calc}=0.295$ ; c.p.=2.074), however, this difference has no statistical significance ( $D_{max}=0.140$ ; c.p.=0.163).

**Table 1** - Distribution of patients according to sex and disease (Jan/62-Mar/85).

Sex	Patients with erythroderma (Jan/62-Mar/85)		Patients without erythroderma (Jan/62-Dec/78)	
	n	%	n	%
Masculine	162	65.6	25,750	44.4
Feminine	85	34.4	32,256	55.6
Total	247	100.0	58,006	100.0

Although, when patients were sub-divided into sub-groups of 5 year periods (Table 2), according to the time of the first visit, a significantly higher number of masculine patients with erythroderma was found (Table 2; 1st. 5 year-period:  $\lambda^2_{calc}=5.156$ ; 2nd. 5 year-period:  $\lambda^2_{calc}=15.751$ ; 3rd. 5 year-period  $\lambda^2_{calc}=10.309$ ; c.p.=3.841).

Table 3 shows no differences by sex among patients without erythroderma who sought assistance in the outpatient clinic.

**Table 2** - Distribution of patients in sub-groups of 5-year periods (Jan/62-Mar/85).

Year	Patients with erythrod		Patients without erythrod	
	Masculine n(%)	Feminine n(%)	Masculine n(%)	Feminine n(%)
1962-1966	10(0.1)	2(0.0)	7,335(99.9)	8,449(99.9)
1967-1971	24(0.3)	5(0.1)	6,876(99.6)	8,619(99.9)
1972-1976	28(0.3)	12(0.1)	8,313(99.7)	10,777(99.9)
1977-1981	55	36	*	*
1982-1985#	45	30	*	*
Total	162	85	22,524	27,845

# 4 year interval  
 \* not reported

\* Personal communication of Bruce B. Duncan, D. Rumel, M.I. Schimidt, 1988.

**Table 3** - Distribution of new cases according to sex, age and year of first visit (Jan/62-Dec/78).

Age (years)	0 - 15		16 - 60		61 +		Total	
	M	F	M	F	M	F	M	F
Year \ Sex								
1962	328	331	647	738	68	88	1,043	1,157
1963	498	520	828	957	116	117	1,442	1,594
1964	491	553	822	1,093	105	124	1,418	1,770
1965	663	660	1,046	1,269	151	169	1,860	2,098
1966	487	492	934	1,193	151	145	1,572	1,830
1967	448	493	956	1,126	146	171	1,550	1,790
1968	433	457	782	983	113	154	1,328	1,594
1969	378	437	739	936	126	136	1,243	1,509
1970	442	453	772	1,118	134	179	1,348	1,750
1971	429	547	846	1,247	132	182	1,407	1,976
1972	579	569	1,008	1,356	152	177	1,739	2,102
1973	598	680	1,006	1,486	190	199	1,794	2,365
1974	437	492	879	1,319	158	220	1,474	2,031
1975	488	504	991	1,448	151	203	1,630	2,155
1976	425	471	1,075	1,446	176	207	1,676	2,124
1977	375	376	975	1,454	157	204	1,507	2,034
1978	519	575	1,197	1,683	165	204	1,881	2,462
Total	8,018	8,610	15,503	20,852	2,391	2,879	25,912	32,341

M - masculine  
F - feminine

The patients with erythroderma (Table 4) showed the following distribution: in the group of from 0 to 15 years old, there was a predominance of feminine patients (Goodman G statistics=3.790; c.p.=2.448), and amongst those over 61 years of age, there was a predominance of masculine patients (Goodman G statistics = 2.571; c.p. = 2.448). The highest number of patients was found to be in the group of from 16 to 60 years old.

**Table 4** - Distribution of patients with erythroderma according to sex and age (Jan/62-Mar/85).

Age (years)	Masculine	Feminine	Total
0 - 15	8	20	28
16 - 60	120	57	177
61 +	34	8	42
Total	162	85	247

Amongst the masculine group (Table 5), erythroderma was more frequent in the group of from 60 to 69 years old (Goodman G statistics=3.885; c.p.=3.751), while amongst the female group it was more frequent in the 10 to 19 year age group.

The majority of the patients were born in S. Paulo state (44.6%), in spite of the fact that the patients' places of birth have not been recorded in about 40.0% of the cases (Table 6).

**Table 5** - Distribution by decades of patients with erythroderma according to sex and age (Jan/62-Mar/85).

Age (years)	Masculine	Feminine	Total
0 - 9	6	10	16
10 - 19	4	17	21
20 - 29	25	13	38
30 - 39	25	16	41
40 - 49	34	11	45
50 - 59	31	9	40
60 - 69	24	3	27
70 +	13	6	19
Total	162	85	247

**Table 6** - Birth places of patients with erythroderma (Jan/62 - Mar/85).

Place of birth	Patients	
	n	%
S. Paulo City	55	22.3
S. Paulo State	55	22.3
Brazil (other states)	37	15.0
Other countries	2	0.8
No information	98	39.6
Total	247	100.0

Applying the Goodman's test to Table 7 (Goodman's  $\gamma^2=2.448$ ; c.p.=12.592), no significant difference was found among the ratio of various causes, by sex.

**Table 7** - Distribution of patients with erythroderma according to clinical manifestation and sex sub-groups, by total numbers (n) and percentages (%) (Jan/62 - Mar/85).

Diagnosis	Patients					
	n			%		
	M	F	T	M	F	T
<i>Previous dermatoses</i>						
Psoriasis	71	40	111	43.8	47.1	44.9
Non atopic eczema	4	1	5	2.5	1.2	2.0
Atopic eczema	9	5	14	5.6	5.9	5.7
Seborrheic eczema	2	2	4	1.2	2.3	1.6
Lamellar ichthyosis	6	3	9	3.7	3.5	3.6
Pityriasis rubra pilaris	1	-	1	0.6	-	0.4
Darier's disease	1	-	1	0.6	-	0.4
Progressive symmetric erythrokeratoderma	-	1	1	-	1.2	0.4
Subtotal	94	52	146	58.0	61.2	59.0
<i>Drug use</i>						
Contact dermatitis	4	1	5	2.5	1.2	2.0
Skin eruption	5	6	11	3.1	7.0	4.5
Photosensitivity	1	1	2	0.6	1.2	0.8
Subtotal	10	8	18	6.2	9.4	7.3
<i>Association with reticulosis</i>						
Lymphoma	5	2	7	3.1	2.4	2.9
Sézary's syndrome	3	-	3	1.9	-	1.2
Subtotal	8	2	10	5.0	2.4	4.1
<i>Miscellaneous</i>						
Nodular scabies	-	1	1	-	1.2	0.4
<i>Unknown causes</i>						
Unknown causes	50	22	72	30.8	25.8	29.2
Total	162	85	247	100.0	100.0	100.0

M - masculine  
 F - feminine

A group of men between the 3rd and 6th decades, inclusive, of life, and of women between

1st and 5th decades, inclusive, with psoriasis, was identified. Cutaneous eruption caused by the use of drugs was more frequent between the 2nd and 5th decades in both sexes (Table 8).

**Comments**

In the literature, there are few notes analyzing erythroderma under its multiple aspects (Abrahams et al<sup>1</sup>, Adam<sup>2</sup>, Gatti et al<sup>6</sup>, Gentile et al<sup>7</sup>, Hasan & Jansen<sup>9</sup>, Montgomery<sup>12</sup>, Nicolis & Helwig<sup>14</sup>, Nigam et al<sup>15</sup> and Rabello et al).<sup>16</sup>

Initially, the group of patients with erythroderma and the group of patients with other dermatosis were compared, in an attempt to find a sampling bias that might have resulted in a higher number of masculine patients in the group with erythroderma.

As no difference by sex was found when the population without erythroderma was studied (Table 1 and 3), it was concluded that the predominance of masculines in the group with erythroderma was not due to any sampling bias. This result is in agreement with those of other authors, ranging from 2: 1 (Adam<sup>2</sup>) to 11: 1 (Nicolis & Helwig).<sup>14</sup>

In more than 59.0% of the total cases there had been a prior manifestation of some dermatosis, of these cases, 44.9% had had psoriasis, 4.0% reticulosis/leukemia, and about 30.0% unknown causes (Table 7), with no difference among the ratio of the various causes according to sex. Therefore, in this population, the underlying disease was not responsible for the difference observed between the sexes in the group of patients with erythroderma (2 masculine: 1 feminine).

The literature shows that there is a predominance of some dermatosis as a prior manifestation in the group of patients with erythroderma (Abrahams et al<sup>1</sup>; Adam<sup>2</sup>; Gatti et al<sup>6</sup>, Gentile et al<sup>7</sup> and Hasan & Jansen).<sup>9</sup> In literature, psoriasis is the

**Table 8** - Distribution of patients with erythroderma, according to age, sex and diagnosis at the last visit (Jan62-Mar/85).

Diagnosis	Sex	Age (years)												Total					
		0 - 9		10 - 19		20 - 29		30 - 39		40 - 49		50 - 59		60 - 69		70 +		M	F
		M	F	M	F	M	F	M	F	M	F	M	F	M	F				
Psoriasis		1	5	1	11	14	7	15	4	16	5	9	5	9	2	6	1	71	40
Drug use eruption		-	-	1	1	1	1	-	3	1	1	2	-	-	-	-	-	5	6
Atopic dermatitis		-	-	-	2	2	-	7	-	-	2	-	1	-	-	-	-	9	5
Unknown causes		2	-	2	1	6	4	-	7	12	4	14	-	9	1	5	5	50	22
Others		3	3	1	2	2	2	3	2	6	-	5	2	5	-	2	1	27	12
Total		6	8	5	17	25	14	25	16	35	12	30	8	23	3	13	7	162	85

M - masculine  
 F - feminine

most frequent dermatosis (25.0 to 60.0%), although no *sensu strictu* comparisons between the literature and our data could be made, since the diagnosis and criteria of inclusion varied so much. This is perhaps the cause of the predominance of cases of drug reaction in Nicolis & Helwig's study<sup>14</sup> and the great number of cases of reticulosis in Montgomery's study<sup>12</sup>.

The frequency of unknown causes with erythroderma varied from 8.0% (Montgomery)<sup>14</sup> to 55.0% (Rabello),<sup>16</sup> against 29.0% in this present study. It is interesting to note that Montgomery<sup>12</sup> had undertaken more skin biopsies than any other author.

It is not easy to compare the data of cases related to the use of drug in the present study with those recorded in the literature because of the great number of drugs involved and the difference in the criteria of inclusion. There are many available drugs and they vary from one country to another and from one time to another, as observed by Nigam et al<sup>15</sup>. Moreover, some authors consider any drug used before the appearance of erythroderma as the causal agent, whereas others do not do so when a primary dermatosis is present.

Only 19.4% of the cases gave any information regarding to the use of drugs prior to the development of erythroderma, and even in these cases, no information about the means of administration or dosage was available. The history of the use of corticosteroid just before the manifestation of erythroderma raised the question as to a possible cause in the inadequate treatment of a previous dermatosis.

All six patients involved with agrototoxic products were men (Tables 9 and 10) of from 30 to 60 years old and came from the countryside. In spite of the small sample, it was asked whether environmental antigens might not be causally related to

**Table 9** - Places where patients with erythroderma came from with history of drug use before the clinical manifestation of erythroderma (Jan/62-Mar/85).

Drug group	Place of origin			Total
	S. Paulo City	S. Paulo State	Other	
Antibiotics and chemotherapeutic agents	4	2	2	8
Corticosteroids	6	7	2	15
Anti-histamines	4	1	2	7
Agrototoxic products	-	3	3	6
Others	4	7	1	12
<b>Total</b>	<b>18</b>	<b>20</b>	<b>10</b>	<b>48</b>

**Table 10** - Distribution of patients with erythroderma with a history of drug use according to sex and drug type (Jan/62-Mar/85).

Drug group	Masculine	Feminine	Total
Antibiotics and chemotherapeutic agents	4	4	8
Corticosteroids	10	5	15
Anti-histamines	2	5	7
Toxic products	6	-	6
Others	7	5	12
<b>Total</b>	<b>29</b>	<b>19</b>	<b>48</b>

erythroderma, and whether the predominance of masculine patients amongst the group with erythroderma could be due to their work-related exposure to the environmental antigens.

One hundred seventy three skin biopsies (1 to 3 biopsies/patient) were performed. Ninety-eight biopsies (about 60.0%) were either diagnostic or suggestive of the underlying diseases, and 75 biopsies (about 40.0%) were non-diagnostic (Table 11).

**Table 11** - Comparison between clinical diagnosis and histopathologic results in patients with erythroderma (Jan/62-Mar/85).

Clinical diagnosis	Histopathologic Results						Total
	CD/SAD*	CD/SAD psoriasiform	Psoriasis	Vasculitis	Suggestive of lymphoma	Others	
Psoriasis	19	23	20	-	-	2	64
Atopic eczema	2	1	-	-	-	-	3
Drug eruption	1	2	-	4	-	1	8
Erythroderma (unknown causes)	33	14	6	8	3	11	75
Others	8	4	1	-	1	9	23
<b>Total</b>	<b>63</b>	<b>44</b>	<b>27</b>	<b>12</b>	<b>4</b>	<b>23</b>	<b>173</b>

\* CD = chronic dermatitis  
SAD = subacute dermatitis

The data from this research corroborate the previous findings of Montgomery's 1933 study<sup>12</sup> that skin biopsies, when performed in sufficient numbers, and under appropriate conditions, are still the best mean of diagnosis and follow-up for patients with erythroderma. Skin biopsy is specially useful in the diagnosis or exclusion of an early reticulosis, since the latter process shows earlier changes in the skin than in other organs (Montgomery).<sup>12</sup>

Another biopsy is recommended when a patient shows a poor therapeutic response and when the

histologic feature is not cleared-up, as may happen the differential diagnosis of Sézary's erythroderma versus pre-Sézary's erythroderma, mycosis fungoides versus persistent reaction to insect bites, and nodular scabies versus mycosis fungoides or Hodgkin's lymphoma (Montgomery).<sup>12</sup>

In striving for an ideal biopsy, the following advice from Montgomery<sup>12</sup> should always be kept up in mind: whenever possible, biopsies should be done on an untreated active area, away from the abdomen or seborrheic areas.

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## Resumo

Foi analisado o perfil de 247 doentes com eritrodermia em um período de 23 anos, de janeiro de 1962 a março de 1985, com o período de seguimento variando de 1 a 26 anos. Os doentes se apresentavam com eritema universal, descamação e prurido com mais de 2 meses de duração e a idade variava de 16 a 60 anos. A psoríase foi a doença associada mais freqüente, com uma proporção estimada de 44,9%, as reações cutâneas ao uso de drogas contribuíram com 7,3% do total de casos e a associação com reticuloses mostrou uma proporção de 4,1%. A eritrodermia permaneceu como de causa desconhecida em 29,2% dos casos. Não foram observadas diferenças entre os sexos no que diz respeito à doença associada. Um ou mais resultados anátomo patológicos das biópsias de pele, em conjunto com o quadro clínico, foi diagnóstico ou sugestivo do diagnóstico da doença associada em 63,6% dos casos. Recomendam-se biópsias de pele seriadas como o melhor método para a elucidação diagnóstica da eritrodermia. Ao nível de significância  $P=0,05$ , foi encontrada uma proporção homem/mulher de 2 : 1. Especula-se se o agente causal da eritrodermia estaria relacionado à exposição diferenciada entre os sexos a antígenos do meio ambiente.

*Dermatite esfoliativa, epidemiologia. Incidência.*