ERYTHRODERMA: INPATIENT SERIES AND REVIEW OF LITERATURE

ERITRODERMIA: SÉRIE DE CASOS INTERNADOS E REVISÃO DA LITERATURA

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ABSTRACT

Erythroderma is rare and potential serious disease that involves desquamation and erythema of more than 90% of the body surface area. It is challenging to find the underlying cause. This report aims to describe epidemiological, clinical-histopathological and therapeutic data of 13 inpatients over the age of 18 in a Dermatology ward of an university hospital. Age, gender, comorbidities, length of stay, hospital-acquired infection, transfer to the intensive care unit and mortality were evaluated. The patients were submitted to three random skin biopsies for histopathological exam, to prednisone treatment (1mg/kg), and a one year follow-up. Eight women (61%) and five men (38%) with a median age of 69 years had arterial hypertension and diabetes *mellitus*; the mean length of hospital stay was 24 days; three patients were transferred to the intensive care unit with hospital-acquired infection, and two died. Seven were idiopathic with no response to treatment; among four cases of psoriasis, three showed remission; among two cases possibly related to drug ingestion, in one case a therapeutic response to prednisone was observed. Erythroderma was highlighted by the lack of etiologic clarity, long evolution, and unsatisfactory therapeutic response to prednisone.

KEYWORDS: **Inpatients; Hospital Medicine; Skin Diseases; Dermatitis Exfoliative.**

RESUMO

Eritrodermia é doença rara e potencialmente grave, que se caracteriza por descamação e eritema em mais de 90% da superfície corporal. A investigação da causa subjacente é desafiadora. Este relato descreve dados epidemiológicos, clínico-histopatológicos e terapêuticos de 13 pacientes acima de 18 anos internados em enfermaria de Dermatologia de um hospital universitário. Idade, gênero, comorbidades, tempo de permanência, infecção hospitalar adquirida, taxas de transferência para a unidade de tratamento intensivo e mortalidade foram analisados. Os pacientes foram submetidos a três biópsias aleatórias de pele (abdômem, dorso e membros) para exame histopatológico, ao tratamento com prednisona (1mg/kg) e ao seguimento por um ano. Oito mulheres (61%) e cinco homens (38%) com idade mediana de 69 anos apresentavam hipertensão arterial e diabetes *mellitus*; o tempo médio de permanência hospitalar foi 24 dias; dos três pacientes transferidos para a unidade de cuidados intensivos por infecção hospitalar adquirida, dois evoluíram para óbito. Sete pacientes idiopáticos sem resposta ao tratamento; entre quatro casos de psoríase, três evoluíram com remissão; entre dois possivelmente relacionados aos medicamentos, houve resposta terapêutica à prednisona em um caso. A eritrodermia se destacou pela etiologia duvidosa, longa evolução e resposta insatisfatória à prednisona.

PALAVRAS-CHAVE: Pacientes Internados; Medicina Hospitalar; Dermatopatias; Dermatite Esfoliativa.

1. INTRODUCTION

Dermatology is primarily a clinical specialty centered on non-acute outpatients, but a substantial number of them need hospitalization for proper management. Patients can benefit from hospital admission in several ways: clinical and laboratory monitoring, parenteral therapy, advanced nursing care, and multidisciplinary care[1].

Erythroderma or exfoliative dermatitis is a syndrome characterized by erythema and scaling involving 80 to 90% of the body surface. The most frequent cause is psoriasis followed by eczematous conditions, drug-induced reactions, pityriasis rubra pilaris, and cutaneous T-cell lymphomas. Edema in extremities, tachycardia, dehydration, electrolytic disorders, protein loss, and body temperature regulation disorders are the most frequent clinical findings in this rare and potentially serious disease. Itching is observed in up to 90% of the cases. The colonization of the skin by *Staphylococcus aureus* is common[2,3]. There are gaps in the scientific literature about the evolution and treatment of the idiopathic type[4,5].

The objective of this study is to describe the epidemiological, clinical, and histopathological profile of erythrodermics admitted to a Dermatology ward.

2. MATERIAL AND METHODS

Age, gender, comorbidities, length of stay, hospital-acquired infection, transfer to the intensive care unit (ICU) and mortality rates were investigated in 13

inpatients over the age of 18. They were submitted to random skin biopsies (abdomen, dorsum, upper or lower limb) for skin histopathological exam, therapy with prednisone (1mg/kd/day), and a one-year follow-up.

The criteria for hospitalization were severe dermatological disease, the need for nursing care, non-adherence or unsatisfactory results to outpatient treatment.

The study was approved by the Research Ethics Committee of Hospital Universitario Clementino Fraga Filho / Universidade Federal do Rio de Janeiro, number CAAE 30128720.8.0000.5267.

3. RESULTS

Eight women and five men with a median age of 69 years, two comorbidities mean, the most frequent being diabetes *mellitus* and arterial hypertension and median hospital stay of 24 days were studied. The duration of illness between three months and one year was present in all patients. Hospital-acquired infections were identified in three patients who were transferred to ICU with blood stream infection in which the isolated agent was *Staphylococcus aureus*: a 66-year old female with systemic arterial hypertension, diabetes *mellitus*, chronic renal disease, obesity, erythrodermic psoriasis, and death; a 63-year old female with erythroderma induced by drug (possible) and death; a 70-year old female with obstructive chronic pulmonary disease, drinking, smoking, erythroderma induced by drug (possible) with remission of her dermatosis.

Histopathological examination was non-specific (cases 1, 2, 3, 4, 5, 6, and 7), compatible for psoriasis (cases 8, 9, 10 and 11), and suggestive from drug use (cases 12 and 13) (Table 1). The histopathological diagnosis of psoriasis was supported by the presence of acanthosis, diffuse parakeratosis, diffuse hypogranulosis and neutrophils on epidermis and dermis; the lichenoid infiltrate supported the drug etiology.

Causality for drugs was classified as possible for NSAID (cases 1, 5), ASA (case 3), captopril (cases 4, 6, 12), carbamazepine (cases 7, 9), and thiazide diuretic (case 13). Solid and hematological neoplasms were excluded through laboratory and imaging tests. Lymph node biopsy was not indicated due to the absence of lymph node enlargement in all cases. No response to prednisone in nine cases (1, 2, 3, 4, 5, 6, 7, 8, and 13) in the follow-up period. Remission in cases 10, 11 (psoriasis); case 12 (possible link to drug), and in case 9 (use of carbamazepine plus suggestive histopathology of psoriasis) (Table 1). Suspected drug discontinuation was possible in all cases.

4. DISCUSSION

Erythroderma usually occurs in the sixth decade with our study being in accordance with the literature concerning age. The average age of onset varies from 41 to 61 years old and reports favor a male predominance[2]. We observed a male to female ratio of 5:8[2]. Four patients suffering from arterial hypertension were diagnosed with possible drug induced erythroderma. In a previous study of 103 patients anti-hypertensive drugs were not implicated[3].

The length of hospital stay for erythrodermics is variable. In our study it was 24 days to 21 days of the other inpatients. A previous investigation refers that regardless of the etiology, the lenght was significantly longer than of other inpatients[3].

Three patients acquired a hospital infection confirming that erythroderma can be life threatening. *Staphylococcus* sepsis may occur due to inflamed and excoriated skin[2].

In erythrodermics, clinical and histopathological correlation can be difficult to attain. Previous studies report skin biopsies to be useful in 53-66% of cases. Frequent histopathologic findings include hyperkeratosis, acanthosis, spongiosis, and perivascular inflammatory infiltrate[2], although the histopathological markers are not consensually established. Perivascular infiltrate with eosinophils, interface dermatitis with necrotic keratinocytes in cases related to drugs[3].

Skin samples are usually obtained with 4mm punch biopsies and over time can enhance diagnostic accuracy. Although a mandatory step in erythrodermics, the number and areas of choice have not yet been defined[5]. In the present series, the histopathological pattern remained unchanged in two subsequent biopsies; the lichenoid or perivascular interface lymphohistiocytic infiltrate pointed to a possible drug reaction, while the psoriasiform and spongiotic focal pattern of tissue reaction (associated with pigmentary incontinence, hemorrhage, and rare eosinophils) did not allow to establish the cause (Table 1). Nonspecific histopathological aspects were observed in a considerable number of cases (39.1%)[2].

Recent retrospective study reported drug-induced erythroderma being diagnosed in 8.5% of subjects with biopsies showing lymphocytes and colloid bodies, in addition to hydropic degeneration within the epidermal basal layer[6]. The authors conclude that erythroderma remains a condition difficult to study and treat.

In the present series, nine cases were considered possibly drug related. The described features of common causes of drug-induced cases (11.3% - 21.6%) are exfoliative scale preceded by morbiliform eruption, face edema, pruritus that commonly resolves two to six weeks after discontinuation of offending drugs and eosinophilia. In the present study, the cases possibly related to drugs did not present this clinical picture. In the two cases with lichenoid infiltrate plus possible causality there was remission in one case after one year of treatment with prednisone thus revealing the complexity of the etiologic definition in this condition (Table 1).

The Naranjo algorithm is commonly used in assessing the causal relationship between drug/adverse events. Even in epidemiological studies, a statistically significant result will provide an estimate as to the probability of an event being caused by a drug but does

not rule out a causal relationship with other determinants[7]. The following criteria were scored and summed up: previous study on adverse reaction; administration of the drug followed by reaction; existence or not of other causes capable of determining the appearance of the reaction; detection of the drug in blood or other organic liquid in concentrations considered toxic; relationship between reaction intensity/increase or decrease of dose; history of reaction similar to the same drug or similar drug; and confirmation of adverse reaction through some objective evidence. The relationship between the onset of erythroderma and the antecedent of intake of the suspected drug as well improvement following the withdrawal of the drug is rather challenging to prove by the usual concomitance of two or more drugs.

Table 1. Erythroderma (n=13).

Case	Age / Gender	Drug	Histopathology	Causality	Treatment/Prednisone	
					Follow-up	Response
1	92 F	NSAID	Psoriasiform dermatitis	Possible	12 months	0
2	86 M	----	Psoriasiform dermatitis	----	12 months	0
3	76 M	ASA	Psoriasiform dermatitis	Possible	12 months	0
4	70 F	Captopril	Psoriasiform dermatitis	Possible	12 months	0
5	68 M	NSAID	Psoriasiform dermatitis	Possible	12 months	0
6	63 F	Captopril	Psoriasiform dermatitis	Possible	Death	0
7	59 F	Carbamazepine	Psoriasiform dermatitis	Possible	12 months	0
8	66 F	----	Psoriasis	----	Death	0
9	59 F	Carbamazepine	Psoriasis	Possible	12 months	Remission
10	56 M	----	Psoriasis	----	12 months	Remission
11	21 F	----	Psoriasis	----	12 months	Remission
12	70 F	Captopril	Lichenoid infiltrate	Possible	12 months	Remission
13	69 M	Thiazide diuretic	Lichenoid infiltrate	Possible	12 months	0

Source: Dermatology ward, Hospital Universitario Clementino Fraga Filho/Universidade Federal do Rio de Janeiro.

Drugs with greatest erythroderma inducing potential are anti-epileptic (carbamazepine) medications and allopurinol. The high frequency of carbamazepine as a cause of erythroderma could be the result of genetic sensitivity to this drug or high prescription rate. Other common drugs related to this condition are phenytoin, beta-lactam antibiotics, sulfonamides, phenobarbital and proton pump inhibitors[3]. In cases series, drug-related reactions represent the second most frequent cause of erythroderma, ranging from 11.3% to 21.6% of cases[3].

In the present study, the algorithm was applied with a possible causality result (1-4 points) for anti-inflammatory drugs, ASA, captopril, carbamazepine, and thiazide diuretic, which have already been recorded in literature[2,3]. The diagnosis of possible cutaneous adverse reaction should be in accordance with definition provided by WHO: a clinical event, including laboratory test abnormality with a reasonable time relation to administration of the drug, but which could also be explained by concurrent disease or other drug or chemicals. Information on drug withdrawal may be lacking or unclear. Hydrochlorothiazide and furosemide have a chemical structure of sulfonamide and captopril has a sulfhydryl radical. Erythroderma secondary to drug reactions has a time interval between the introduction of the drug and the onset of the disease of 1-6 weeks[2]. It can improve or resolve within 2-6 weeks of drug discontinuation. The difficulty in the therapeutic management of suspected drug-related cases becomes crucial when it is impossible to replace or to stop taking it. Our cases showed a slow and dragged-out course (even with drug discontinuation) that seriously compromised the quality of life.

The proportion of cases of idiopathic erythroderma vary between 3.9% and 25.6% or 6.51% and 36%[2,3]. In the present study, no precise etiology could be identified in seven of the 13 cases.

Failure to thrive is a clinical clue for idiopathic or paraneoplastic erythroderma. In our study, the screening for neoplasia was guided by the profile age, gender, frequency, signs, and symptoms. None of the patients presented malignancies.

To date, there are no guidelines for the treatment of idiopathic erythroderma[8]. Oral corticosteroids, cyclosporine, ultraviolet therapy, or a combination of these therapies have been proposed. We observed a slow or refractory response to prednisone for a period of one year when suspicious drugs had already been suspended (cases 1, 3, 4, 5, 7, and 13). One study obtained follow-up information (median of 4 years) from drug related (n=19) and idiopathic erythroderma (n=4) groups. No relapse was observed in both groups; the treatment is not mentioned[3]. Subjects with idiopathic erythroderma can exhibit complete remission (30%) or partial remission (50%).

Use of systemic steroids is controversial as withdrawal may precipitate an erythrodermic flare, but patients with idiopathic erythroderma who fail to

respond to topical treatments should be treated with systemic corticosteroids. A recent retrospective population-based cohort study found that 30.8% of patients with erythrodermic psoriasis and 39.6% with erythroderma died within the first three years following hospital admission[9].

In the present series, we chose to use prednisone for the possibility of a faster response, availability of the drug, to protect the body's hemodynamics and to prevent infections from the skin.

Low mortality rates (1% to 3.8%) is reported in studies from recent decades[2,3]. Our findings were two (15%) deaths in the first year of follow-up: one erythrodermic psoriasis and one drug related. The role of comorbidities seems clear to us (Table 1).

Sepsis was described to occur in 40 (4.65%) inpatients in the Dermatology ward. The frequency was highest in toxic epidermal necrolysis (90%) followed by drug-induced maculopapular rash (20%), erythroderma (17.5%), and vesiculobullous diseases (8.5%). In vesiculobullous disorders or erythroderma, *Staphylococcus aureus* (MRSA) was the predominant isolate in the blood[10]. Our findings (3/23%) are close.

In the present investigation, nine cases (cases 1, 2, 3, 4, 5, 6, 7, 8, and 13) failed to respond to treatment with prednisone. Patients with idiopathic erythroderma who fail to respond to systemic corticosteroid may be treated with other immunosuppressants such as methotrexate or cyclosporine; however, evidence for this approach is scarce[11,12].

5. CONCLUSIONS

The Dermatology ward played an essential role in assisting the dermatological patients in a tertiary hospital. Our cases were highlighted by morbidity, difficulties in etiologic diagnosis, and challenging treatment; literature review pointed gaps in the knowledge of idiopathic erythroderma that future studies should address.

6. REFERENCES

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