Histological patterns of cutaneous adverse drug reactions

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Abstract

Cutaneous adverse drug reactions (ADR) are skin conditions due to a drug, regardless of the way of administration. Knowledge about their frequency, clinical manifestations and histopathological patterns is essential for prevention and early diagnosis, avoiding complications and reducing morbidity. This work assessed the incidence of cutaneous ADR in skin biopsies from patients with inflammatory dermatoses, and determined their histopathological patterns. Skin biopsies from patients with inflammatory dermatoses, obtained in the years 2006-2007 at the Pathology Division of the HU/UFJF, were analyzed. The different histopathological patterns were grouped, the cases were statistically analyzed and a clinicopathological matching was attempted. Of the 1409 skin biopsies, 304 cases of inflammatory dermatoses were diagnosed, 31 corresponding to cutaneous ADR. The most frequent histopathological pattern was vacuolar interface dermatitis (41.9%). The most frequently involved drug was captopril. Identification of histopathological patterns and anatomoclinical correlation are indispensable for the differential between cutaneous ADR and the other inflammatory dermatoses, allowing for an early and precise diagnosis and reducing treatment and hospitalization costs.

Keywords: Drug Eruptions. Drug Toxictiy. Pathology. Skin/drug effects.

1 Introduction

The WHO (1969) defines an adverse drug reaction (ADR) as "any noxious, unintended, and undesired effect of a drug that occurs at doses used in humans for prophylaxis, diagnosis or therapy" (ALONZO; LÓPEZ, 2000). Although any organ may be a target to an ADR, the skin is most commonly affected because of its metabolic and immunological functions. Thus, cutaneous ADR are diseases of the skin and/or mucous membranes, with or without systemic involvement, caused directly or indirectly by drugs administered orally or parenterally, regardless of the dose (UNIFESP, 2006).

With the rapid development of new therapeutic agents, new cases of cutaneous ADR are diagnosed every year. Even though any medication can potentially cause an adverse cutaneous reaction, some drugs are implicated more commonly than others (JUSTINIANO; BERLINGERI-RAMOS; SÁNCHEZ, 2008). The drugs most frequently responsible for these reactions are penicillins (chiefly aminopecinillins), sulphonamides, aromatic anticonvulsants (phenytoin, carbamazepin, phenobarbital), non-steroidal anti-inflammatory drugs (NSAIDs) of the oxicam group (piroxicam, tenoxicam), ACE-inhibitors, hydralazine and haloperidol (SILVA; ROSELINO, 2003).

International studies point to a 2-3% incidence of cutaneous ADR clinically diagnosed in inpatients worldwide (ARNDT; HERSHEL, 1976). ADR are the most common iatrogenic reactions, complicating 5-15% of all drug treatments. 100,000 deaths/

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year are attributed to ADR in the United Sates (RIEDL, 2003). 3-6% of all hospital admissions are due to ADR, and of all hospitalized patients (2.2 million in the USA in 1994), 6-15% suffered such reactions (AZULAY; AZULAY, 2008). One example of cutaneous ADR is toxic epidermal necrolysis (TEN), whose high case-fatality rate (30-40%) is a reminder of the potential severity of cutaneous ADR (SAMPAIO; RIVITTI, 2007). Because they are so frequent, ADR must be better studied, so that an early diagnosis can be made, complications avoided and morbidity reduced.

Cutaneous ADR may be classified according to pathogenesis and clinical morphology. As for pathogenesis and pathophysiology, immunologic and non-immunologic reactions may occur. Immunologic cutaneous ADR are also called drug allergies. According to the Gel-Combs`classification, these reactions may be: type I (IgE-mediated), type II (cytotoxic), type III (immune complexes-mediated) and type IV (cell-mediated). Non-immunologic mechanisms may result from adverse drug effects, overdose, cumulative toxicity, side effects, local microflora imbalance, drug interaction, metabolic alterations or intensification of pre-existing skin disorders, idiosyncratic reactions, teratogenicity and the Jarisch-Herxheimer`s reaction (OMAHA, 2006).

Some skin rashes may be associated with systemic involvement (fever, myalgia, leukocytosis, lymphadenopathy, arthralgia, arthritis) and/or multiorgan involvement (hepatitis, nephritis). Yet, because they are more conspicuous, skin changes are more frequently found (OLIVEIRA et al., 1992).

Cutaneous ADR have a wide range of clinical presentations. Clues to the drug-induced nature of the cutaneous eruption include the presence of overlapping histological reaction patterns and incongruent clinical and histopathological features (RAMDIAL; NAIDOO, 2009). Histologically, drugs can elicit a variety of inflammatory disease patterns in the skin and panniculus, no pattern being specific for a particular drug. The most common pattern elicited by systemically administered medications is the perivascular pattern. Psoriasiform or granulomatous patterns are rarely caused by medications (JUSTINIANO; BERLINGERI-RAMOS; SÁNCHEZ, 2008) Cutaneous changes comprise urticaria, photosensitivity, erythema multiforme, pigmentation disorders, exanthems, fixed pigmented erythema, erythema nodosum, toxic necrolysis, lichenoid rashes, acne-like rashes, bullous reactions and psoriasis-like reactions. These cutaneous manifestations may mimic several dermatological conditions (MACKEE; CALONJE; GRANTER, 2005).

The real incidence of cutaneous ADR is difficult to determine, not only because the patient`s information may be unreliable, but also because some clinical presentations may have other etiologies besides being drug-related. Although cutaneous ADR generally occur two weeks after drug initiation (FARMER; HOOD, 1999), they may be late events, occurring up to six months after drug use and withdrawal, making it impossible to conclusively define a relationship between drug use and cutaneous ADR. Only exceptionally should a challenge with the suspect drug be performed (BEAVEN; BROOKS, 1984).

The course and prognosis of cutaneous ADR are generally favorable. After drug withdrawal skin symptoms subside. Yet some cases may progress to severe systemic involvement with a bad prognosis.

Cutaneous ADR are underdiagnosed in Brazil, mainly because there are not enough systematic studies assessing prevalence and histopathological patterns, something indispensable for an earlier and more precise clinicopathological diagnosis, which would reduce the high cost of equivocal treatments and unnecessary hospital admissions.

This study provides elements for dermatological clinical investigation, allowing for a more efficient clinicopathological correlation to be made.

2 Material and Methods

This was a retrospective study of data and slides of all skin biopsies performed during the years 2006 and 2007, at the Pathology Division of the University Hospital of the Juiz de Fora Federal University (HU/UFJF), Minas Gerais, Brazil. The incidence of diagnoses of drug-related cutaneous ADR was calculated from all diagnoses of inflammatory dermatoses. A classification of cutaneous ADR based on their histopathological patterns was also made. The data bank of the division was assessed and all inflammatory dermatoses diagnoses were identified. Of these, the slides with reports consistent with ADR were selected and the histopathological patterns were defined and systematically classified according to Crowson and Magro (1999).

The medical files of patients with a histopathological diagnosis of cutaneous ADR were searched for data concerning age, gender, clinical manifestations and possibly used drugs. All the cases with a inflammatory dermatoses diagnosis were included in the study. Cases whose diagnoses were related to neoplastic conditions, degenerative diseases and others besides inflammation/immunologic disorders (inflammatory dermatoses) were excluded.

The epi Info program (3.4.3 version, Nov/2007) was used for data analysis. Datasheets and statistical analysis were used to determine the frequencies of the different cutaneous ADR patterns, with an emphasis on identification of predominant patterns, drugs and clinical manifestations. The results obtained were compared by means of the Student's *t* test, $p \leqq 0.05$ being stipulated as significance level.

The study was approved (CAAE 0039.0.180.000-07 protocol) by the National Committee of Research Ethics (Comitê Nacional de Ética em Pesquisa – CONEP) and by the Research Ethics Committee of the HU/UFJF (CEP/UFJF 10050512007 protocol).

3 Results

Of a total of 1409 skin biopsies from the study period, 304 were diagnosed with inflammation. Of these, 31 (10.19%) had a histopathological diagnosis of cutaneous ADR, corresponding to 2.2% of the 1409 skin biopsies.

Of the 31 patients with a histopathological diagnosis of cutaneous ADR, 16 (51.6%) were female and 15 (48.4%) male, no statistically significant difference concerning gender being found (p=0.857) (Table 1).

Table 1

Frequency of cutaneous ADR by gender

Valid	Frequency	%
F	16	51.6
M	15	48.4
Total	31	100.0

p=0.857

Font: The authors (2009).

Age ranged from 1 to 87 years, with higher prevalence in the 61-70 age range (25.8%) (Table 2).

Table 2

Frequency of cutaneous ADR by age

Age	Number	%
0-10	1	3,2
11-20	0	0
21-30	2	6,45
31-40	6	19,35
41-50	1	3,2
51-60	6	19,35
61-70	8	25,8
71-80	6	19,35
81-90	1	3,2
Total	31	100

Font: The authors (2009).

There was no significant variation between the mean age found in males (54.6 years) and that of females (55.5 years) (p=0.906). As for ethnicity, 67.7% were white and 32.3% non-white (p=0.048) (Table 3).

Table 3

Frequency of cutaneous ADR by ethnicity

Ethnicity	Frequency	%
White	2	67,74
Non-white	10	32,25
Total	31	100,0

p = 0.048

Font: The authors (2009).

The most frequent clinical manifestation was popular scaly eczema (54.83%) (p=0.000) followed by erythema multiforme (29.2%), fixed pigmented erythema (9.67%) and ulcerative lesions (6.45%) (Table 4).

Table 4

Frequency of clinical manifestations in cases of cutaneous ADR

Patterns	Subtypes	Frequency	%
Dermatite de interface	Vacuolar	13	41,9
	Lichenoid	4	12,9
	Lichenoid and vacuolar	5	16,1
Psoriasis-like dermatitis	Espongiotic	2	6,4
	Pure	5	16,1
Granulomatous		5	6,4
Total		31	100,0

p=0.001

Font: The authors (2009).

Table 5 shows the frequencies of the histopathological patterns found.

Table 5

Microscopic patterns of cutaneous ADR

	Frequency	%
Erythema multiform	8	29,02
Fixed pigmented erythema	3	9,67
Ulcerative lesion	2	6,45
Papular scaly eczema	17	54,83
Total	31	100,0

p = 0, 001

Font: The authors (2009).

The most prevalent was vacuolar interface dermatitis (41.9%) (p=0.001) (Fig. 1), followed by lichenoid and vacuolar interface dermatitis (Fig. 2), psoriasis-like dermatitis (Fig. 3) and granulomatous pattern (Fig. 4). The least common patterns were lichenoid interface dermatitis (12.9%) and spongiotic and granulomatous psoriasis-like dermatitis (6.4%).

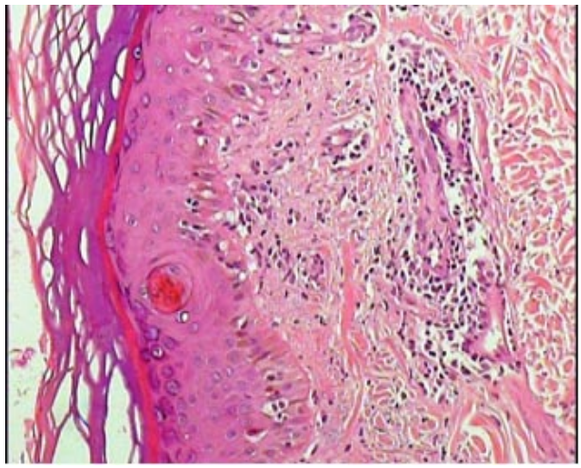

Figure 1: Interface dermatitis. HE 200X.
Font: The authors (2009).

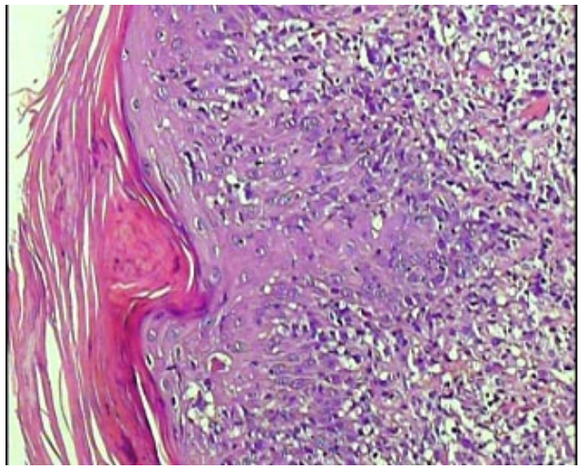

Figure 2: Lichenoid and vacuolar interface dermatitis. HE 200X.
Font: The authors (2009).

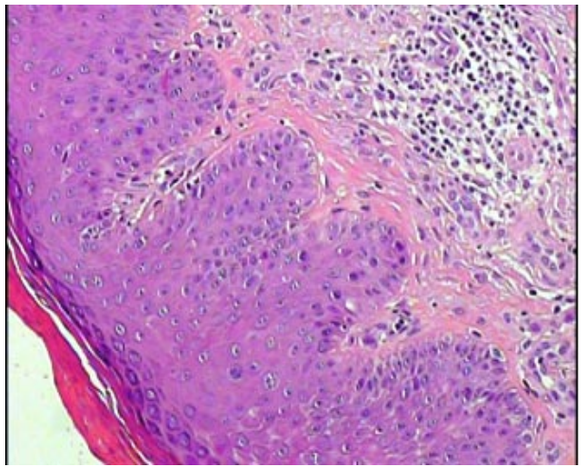

Figure 3: Psoriasis-like dermatitis. HE 200X.
Font: The authors (2009).

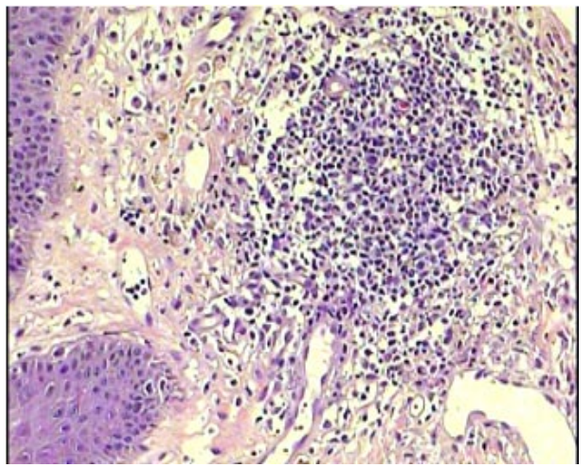

Figure 4: Granulomatous pattern. HE 400X.
Font: The authors (2009).

Captopril (22.6%) was the most frequently used drug among the patients with cutaneous ADR (Table 6).

Table 6

Prevalence of captopril use among patients with cutaneous ADR

User	Frequency	%
No	24	77,4
Yes	7	22,6
Total	31	100,0

Font: The authors (2009).

28.6% of the patients with the vacuolar interface dermatitis pattern reported captopril use (p=0.408) (Table 7).

Table 7

Relationship between vacuolar interface dermatitis pattern and captopril

		Vacuolar Interface Dermatitis		
		No	Yes	Total
Captopril	No	15	9	24
		62,5%	37,5%	100,0%
	Yes	5	2	7
		71,4%	28,6%	100,0%
Total		20	11	31
		64,5%	35,5%	100,0%

p=0,408

Font: The authors (2009).

Table 8 presents the study cases with their clinical presentations, histopathological features and drugs used by each patient.

Table 8

Correlation of clinical manifestations and microscopic patterns

CASES	CLINICAL PRESENTATION	MICROSCOPY	DRUGS
CASE 1	ERYTHEMA MULTIFORME	VACUOLAR INTERFACE DERMATITIS	CHLOROQUINE / PREDNISONE / FOLIC ACID
CASE 2	PAPULAR SCALY ECZEMATOUS LESION	VACUOLAR INTERFACE DERMATITIS	NO REPORT
CASE 3	ERYTHEMA MULTIFORME	LICHENOID INTERFACE DERMATITIS	NO REPORT
CASE 4	ERYTHEMA MULTIFORME	VACUOLAR AND LICHENOID INTERFACE DERMATITIS	NO REPORT
CASE 5	PAPULAR SCALY ECZEMATOUS LESION	VACUOLAR INTERFACE DERMATITIS	CAPTOPRIL / FUROSEMIDE/ NIFEDIPINE / ASPIRIN / SINVASTATIN
CASE 6	FIXED PIGMENTED ERYTHEMA	VACUOLAR INTERFACE DERMATITIS	LAMIVUDIN /ZIDOVUDIN / NEVIRAPIN / OMEPRAZOLE/ VITAMINS OF B COMPLEX
CASE 7	FIXED PIGMENTED ERYTHEMA	VACUOLAR INTERFACE DERMATITIS	NO REPORT
CASE 8	ERYTHEMA MULTIFORME	VACUOLAR AND LICHENOID INTERFACE DERMATITIS	CAPTOPRIL, HYDROCHLOROTHIAZIDE, NIFEDIPIN, CHLORPROMAZINE, CHLOMIPRAMINE, FLUNARIZINE
CASE 9	PSORIASIFORM LESION	PURE PSORIASIS-LIKE DERMATITIS	CARBAMAZEPINE
CASE 10	ULCERATIVE LESION	LICHENOID INTERFACE DERMATITIS	CAPTOPRIL
CASE 11	PAPULAR SCALY ECZEMATOUS LESION	VACUOLAR INTERFACE DERMATITIS	NO REPORT
CASE 12	ERYTHEMA MULTIFORME	PADRÃO GRANULOMATOSO	NO REPORT
CASE 13	PAPULAR SCALY ECZEMATOUS LESION	VACUOLAR AND LICHENOID INTERFACE DERMATITIS	HYDROCHLOROTHIAZIDE, CAPTORIL, ANLODIPINE
CASE 14	PAPULAR SCALY ECZEMATOUS LESION	PADRÃO GRANULOMATOSO	NO REPORT
CASE 15	PSORIASIFORM LESION	PURE PSORIASIS-LIKE DERMATITIS	CAPTOPRIL
CASE 16	ERYTHEMA MULTIFORME	VACUOLAR AND LICHENOID INTERFACE DERMATITIS	NO REPORT
CASE 17	ERYTHEMA MULTIFORME	DERMATITE PSORIASEFORME ESPONGIÓTICA	NO REPORT
CASE 18	FIXED PIGMENTED ERYTHEMA	VACUOLAR INTERFACE DERMATITIS	ALENDRONATE SODIUM,, CAPTOPRIL
CASE 19	PAPULAR SCALY ECZEMATOUS LESION	LICHENOID INTERFACE DERMATITIS	ALPRAZOLAM, CIPROEPTADIN, FLUOXETIN, RACUMIM, CREOLIN
CASE 20	PAPULAR SCALY ECZEMATOUS LESION	DERMATITE PSORIASEFORME ESPONGIÓTICA	MARIJUANA AND COCAINE
CASE 21	PAPULAR SCALY ECZEMATOUS LESION	VACUOLAR INTERFACE DERMATITIS	NO REPORT
CASE 22	PAPULAR SCALY ECZEMATOUS LESION	VACUOLAR INTERFACE DERMATITIS	NO REPORT
CASE 23	PAPULAR SCALY ECZEMATOUS LESION	VACUOLAR INTERFACE DERMATITIS	QT CA PRÓSTATA/CAPTOPRIL/ HYDROCHLOROTHIAZIDE / DIAZEPAN/ RANITIDIN/ AMINOFILIN
CASE 24	PAPULAR SCALY ECZEMATOUS LESION	PURE PSORIASIS-LIKE DERMATITIS	NO REPORT
CASE 25	PAPULAR SCALY ECZEMATOUS LESION	VACUOLAR INTERFACE DERMATITIS	SUSTRATE, CLONAZEPAN, VASTAREL SELOPRESS (METOPROLOL+ HYDROCHLOROTHIAZIDE), ASPIRIN
CASE 26	PAPULAR SCALY ECZEMATOUS LESION	VACUOLAR INTERFACE DERMATITIS	NO REPORT
CASE 27	PAPULAR SCALY ECZEMATOUS LESION	VACUOLAR AND LICHENOID INTERFACE DERMATITIS	CEFALEXINE
CASE 28	PAPULAR SCALY ECZEMATOUS LESION	PURE PSORIASIS-LIKE DERMATITIS	MOTILIUM/LABEL
CASE 29	ERYTHEMA MULTIFORME	VACUOLAR INTERFACE DERMATITIS	DORFLEX,CLONAZEPAN, ALENDRONATE SODIUM , CALCIUM CARBONATE, VITAMIN D
CASE 30	ULCERATIVE LESION	LICHENOID INTERFACE DERMATITIS	NO REPORT
CASE 31	PAPULAR SCALY ECZEMATOUS LESION	PURE PSORIASIS-LIKE DERMATITIS	HYDROCHLOROTHIAZIDE, CAPTOPRIL, NIFEDIPINE, INSULIN

4 Discussion

Drug eruptions are the most commonly observed drug side effects and are a frequent reason for consultation in clinical practice (JUSTINIANO; BERLINGERI-RAMOS; SÁNCHEZ, 2008). They are important causes of morbidity, high hospital costs and even death (FARMER; HOOD, 1999).

Although common, the actual incidence, severity and global effects on health of cutaneous ADR are difficult to determine. This is so because many reactions are so quick and transient that they are simply not diagnosed. At times, patients are on several drugs simultaneously, making it extremely difficult to attribute a given reaction to a particular drug (UNIFESP, 2006). The recognition of drug-related histopathological patterns is thus paramount.

The histopathology-based incidence of cutaneous ADR in this study was 10.19% (31 of 304 skin biopsies diagnosed with inflammation), corresponding to 2.2% of 1409 skin biopsies performed from January 2006 through December 2007. This contrasts with the 12.3% incidence found in 690 dermatological consultations in a general hospital in Porto Alegre (WEISSBLUTH et al., 1984), although that was a clinical study without histopathological correlation. Conversely, our incidence is in accordance with that reported by Arndt and Hershel (1976) and Kauppinen (1972), who found values around 2%. Montgomery and Jackson (1984) reported a 1.66% incidence.

Our study involved outpatients and inpatients. The incidence we found (2.2%) was close to that of a large study of 15,438 inpatients, published in 1986. Of those patients, 358 (2.3%) were diagnosed with cutaneous ADR (BIGBY et al., 1986). Brazilian studies of inpatients and outpatients report a 0.78% to 66.6% incidence range for cutaneous ADR. The lowest frequencies correspond to samples exclusively composed of outpatients, a population in which the use of systemic medications is relatively low. The greater the percentage of inpatients included the higher the incidence of cutaneous ADR (BOPP et al., 1973; PEREIRA et al., 1982; WEISSBLUTH et al., 1984). The 66.6% incidence reported corresponds to 100 patients of a sample of 150 psychiatric inpatients. This unusually high incidence could be accounted for by the use of multiple drug associations in psychiatric patients, perhaps higher than that found in general hospitals (BOPP et al., 1973; WEISSBLUTH et al., 1984). There are no great epidemiologic studies assessing the prevalence of cutaneous ADR in outpatients, but the incidence is thought to range from 1% to 3%, although such figures were obtained from clinical diagnoses only (FARMER; HOOD, 1999).

As for gender, our study did not show any statistically significant difference, as of the 31 patients with cutaneous ADR, 16 (51.6%) were female and 15 (48.4%) male. Yet literature reports a female predominance: 72.3% (FESTA NETO, 1990); 64.5% (KAUPPINEN, 1972); 70.0% (KAUPPINEN; STUBB, 1984); 63.0% (MONTGOMERY; JACKSON, 1984); 58.8% (WEISSBLUTH et al., 1984). Statistically significant differences in cutaneous ADR between men and women were also reported by Arndt and Hershel (1976), who found a 50% higher incidence in women in their 22,227 inpatient sample. Hurwitz (1969) also correlated gender with cutaneous ADR, showing a higher incidence in females ($0.01>p>0.001$). Montgomery and Jackson (1984) reported a proportion of 63 women to 37 men. Only Sushma and others (2005) reported a male predominance (52%).

As for age, our results are compatible with the literature, with a higher incidence in the 31-80 years age range. Most patients were in the 61-70 age range (25.8%) (Table 2). This finding may be explained by chronic age-related cardiovascular and degenerative morbidities or co-morbidities. Weissbluth and others (1984) observed a higher incidence in the 40-50 age range (20%), while Montgomery and Jackson (1984) and Kauppinen (1972) found a higher incidence in the 51-60 age range (23% and 19%, respectively).

As for ethnicity, 67.7% were white and 32.3% non-white (mulatto or black). We found only one report of this factor in the literature. In agreement with our findings, Silvares and others (2008) found 86% white and 14% non-white (mulatto or black) in their sample of 43 patients with cutaneous ADR. No references accounting for this difference were found, however.

Captopril has been reported to induce interface inflammatory dermatoses histopathological pattern and bullous lesions (penfigoid patterns) (FARMER; HOOD, 1999). Of all the drugs causing adverse effects in our study, captopril was the most frequently used (22.6%).

As for the histopathological pattern, the most frequent one was interface dermatitis, with the vacuolar subtype as the most frequently observed pattern (41.9%; $p=0.001$) (Table 5). According to Farmer and Hood (1999), the superficial perivascular dermatitis pattern is the most commonly found, corresponding to a morbilliform skin rash (exanthema and maculopapular lesions) and accounting for 26% to 46% of all drug-related skin lesions. The other commonly found patterns are superficial perivascular and interstitial dermatitis, corresponding to urticaria-like lesions (20% to

23%) and interface dermatitis, corresponding to a fixed drug eruption on a given body site (up to 22% incidence). Our findings, however, showed a statistically significant predominance of the interface dermatitis pattern. It must be taken into account that morbilliform and urticaria-like ADR have an acute clinical course that can be easily related to drug administration, while interface dermatitis can develop lesions within weeks, months or even years of drug use. Within the interface dermatitis pattern there are the vacuolar, lichenoid and vacuolar/lichenoid subtypes, corresponding to a range of clinical presentations: bullous lesions of erythema multiforme, plaque lesions with vesicles or bullae in drug-related fixed eruption and small purplish plaques similar to lichen planus, mimicking dermatitidis of different etiologies. Because of their chronicity and the need to establish a differential diagnosis, such cases more frequently undergo biopsy, a correlation with drug use being difficult to make.

This study showed many patients on several drug regimens and others without any report of drug use, pointing to the difficulty of a clinicoanatomical correlation.

5 Conclusion

The incidence of cutaneous ADR in skin biopsies obtained during the period January 2006-December 2007 was high, and agrees with data from national and international studies. Vacuolar interface dermatitis was the most frequent histopathological pattern, corresponding to chronic lesions that are easily confounded with other inflammatory dermatoses and, because of this very reason, require histopathology for a differential diagnosis. The patients were on several drugs, captopril being the most statistically relevant one. Systematic studies including larger samples are necessary for more adequate clinicopathological correlations.

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Abstract

Cutaneous adverse drug reactions (ADR) are skin conditions due to a drug, regardless of the way of administration. Knowledge about their frequency, clinical manifestations and histopathological patterns is essential for prevention and early diagnosis, avoiding complications and reducing morbidity. This work assessed the incidence of cutaneous ADR in skin biopsies from patients with inflammatory dermatoses, and determined their histopathological patterns. Skin biopsies from patients with inflammatory dermatoses, obtained in the years 2006-2007 at the Pathology Division of the HU/UFJF, were analyzed. The different histopathological patterns were grouped, the cases were statistically analyzed and a clinicopathological matching was attempted. Of the 1409 skin biopsies, 304 cases of inflammatory dermatoses were diagnosed, 31 corresponding to cutaneous ADR. The most frequent histopathological pattern was vacuolar interface dermatitis (41.9%). The most frequently involved drug was captopril. Identification of histopathological patterns and anatomoclinical correlation are indispensable for the differential between cutaneous ADR and the other inflammatory dermatoses, allowing for an early and precise diagnosis and reducing treatment and hospitalization costs.

Keywords: Drug Eruptions. Drug Toxicty. Pathology. Skin/drug effects.

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