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Pharmacodermia after use of Anti-Inflammatory: A Case Report

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ABSTRACT

This case report aimed to show the interference of pharmacodermia in the increased use of anti-inflammatory drugs and evaluate the incidence of drug reactions in patients with evolution to cutaneous manifestations assuming multiple clinical aspects. An elderly patient on continuous use of bronchodilators, anticholinergics, and inhaled corticosteroids was hospitalized for pharmacodermia treatment after the use of anti-inflammatory drugs. The patient was admitted with a history of using Flancox (etodolac) for two days for low back pain, evolving suddenly with pruritic urticarial plaques in the trunk region, migrating to limbs and face. She mentioned being allergic to nimesulide, dipyrone, and penicillin during the anamnesis. The medication was immediately discontinued and intravenous corticosteroids (hydrocortisone 200 mg IV 8/8 h) were started associated with clinical support and antihistamine measures. The patient was discharged after seven days of hospitalization, with clinical improvement and remission of lesions. Corticosteroid suspension was prescribed with prednisone, Hixizine 25 mg, and promethazine.

KEYWORDS: Dermatological side effects; pharmacodermia; hypersensitivity; skin and adverse drug reactions.

INTRODUCTION

Pharmacodermia is an adverse dermatological reaction to a drug, which may cause some side effects related to the skin and/or its annexes. Drug administrations in the treatment or prevention of diseases can cause unexpected adverse reactions, involving different organs or systems. Cutaneous manifestations are the most common, assuming multiple clinical aspects (Sociedade Brasileira de Dermatologia, 2017).

The incidence of drug reactions in hospitalized patients varies from 10 to 30%. Drug use grows progressively, and 5 to 15% of patients treated with some drug are estimated to develop drug skin reactions, which assume different clinical patterns. These reactions are often not serious but can determine morbidity and/or require hospitalization, occurring with a certain frequency due to the ease of acquisition, imprudence in prescribing drugs, and drug overdose (Tavares *et al*., 2016).

Adverse drug reactions are a major problem in medical practice, as they cause hospitalization, sometimes prolonged, morbidity, or mortality. Moreover, they negatively modify the patient's quality of life, contribute to the patient's loss of trust in the health team, increase expenses, and can delay treatment, as they can simulate diseases (Figueiredo *et al*., 2017).

The cluster of diseases in a patient can lead to the overuse of drugs inadvertently, such as low back pain, which is a disease with a multifactorial characteristic, leading to the prescription of drugs of different classes in concomitant use, increasing the chances of adverse reactions.

The diagnosis of pharmacodermia is often difficult due to the great multiplicity of clinical aspects and the similarity with other diseases. The first measures include the suspension of the medication in use and the immediate search for medical assistance. Commonly used antiallergics are not immediately effective, requiring a certain time for the complete improvement of the symptoms until the total elimination of the problem drug from the body. The prognosis is good if there is no reuse of the drug and no extensive necrosis and organ involvement. The prognosis regarding

evolution, cure, and life in general is good in most clinical forms of pharmacodermia (Santos *et al*., 2015).

This case report aimed to evidence the interference of pharmacodermia in the increased use of anti-inflammatory drugs and assess the incidence of drug reactions in patients with the evolution to cutaneous manifestations assuming multiple clinical aspects.

CASE REPORT

Female patiente, 61 years old, with a history of systemic arterial hypertension, asthma, and gastritis, under continuous use of bronchodilators, anticholinergic, and inhaled corticosteroids, was hospitalized on December 29, 2021, for treatment of pharmacodermia after use of anti-inflammatory. She was admitted with a history of using Flancox (etodolac) for 2 days for low back pain, evolving suddenly with pruritic urticarial plaques in the trunk region (Figure 1), migrating to limbs and face. She presented angioedema and complained of dysphagia and ulcerative lesions in the oral mucosa on admission. Admission blood count with leukocytosis, left shift, and eosinophilia. Urine I with leukocyturia (300000) and hematuria (100000), with no urinary or systemic complaints suggesting urinary tract infection. Other laboratory tests were within the normal range. She mentioned being allergic to nimesulide, dipyrone, and penicillin. The medication was immediately discontinued and intravenous corticosteroids (hydrocortisone IV 200 mg 8/8 h) were started associated with clinical support and antihistamine measures. Laboratory tests showed the following results at the time of admission to the emergency care unit (December 29, 2021):

Blood count: hb 13.6/ ht 40.2/ leukocytes 32400 – blasts 0/myelocytes 0/ metamyelocytes 0/rods 648/ segmented 21125/ lymphocytes 6415/ atypical lymphocytes 0/ monocytes 3499/ eosinophils 713/ basophils 0/platelets 152000. Urea 47/ creatinine 1.04/ DHL 460/ arterial blood gas: pH 7.24; PCO_2 70.8; PCO_2 35.7; HCO_3 15.5; TOTAL CO_2 16.6; BE – 10.9; $\%SO_2$ 91.7%; FIO_2 *%/ reactive C-protein 5.17/ sodium 143/ potassium 4.5/ INR 0.98.

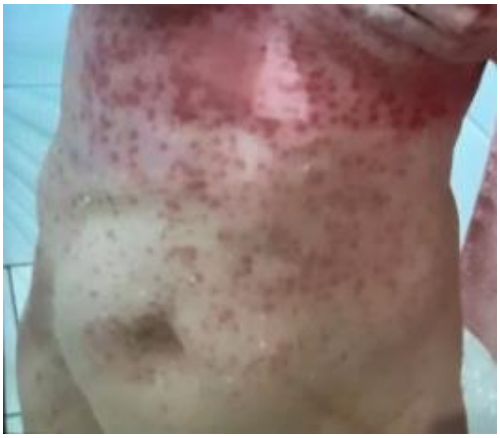

Figure 1. Pruritic urticarial plaques in the trunk region presented by the patient on the admission date (December 29, 2021).

Urticarial lesions with intense pruritus and reddish color in the first days progressed to rosacea, with progressive improvement of pruritus and dysphagia after the proposed treatment (Figures 2 and 3). The patient remained hemodynamically stable during the hospital stay, with no progression to necrosis of the skin lesions and no need for an intensive care bed (Figure 4). A progressive decrease in leukocytosis (24700–19700; probable reactional origin – leukocytes on 12/28 with a value of 9600 and C-reactive protein 1.0) during hospitalization at the Emergency Care Unit (UPA). Eosinophilia decreased from admission (maximum of 926) to discharge (131). Also, decreased evidence of inflammatory activity and negative urine and blood cultures were observed.

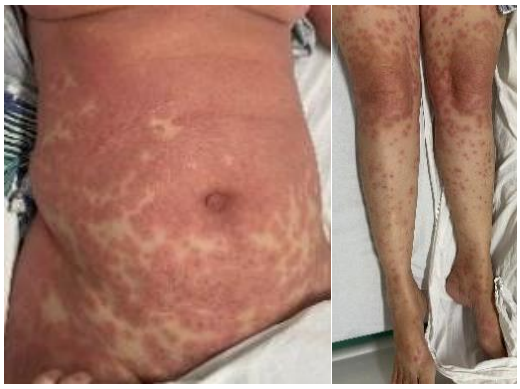

Figure 2. Evolution of pruritic urticarial plaques in different regions of the body after treatment with corticosteroids, recorded on December 30, 2021.

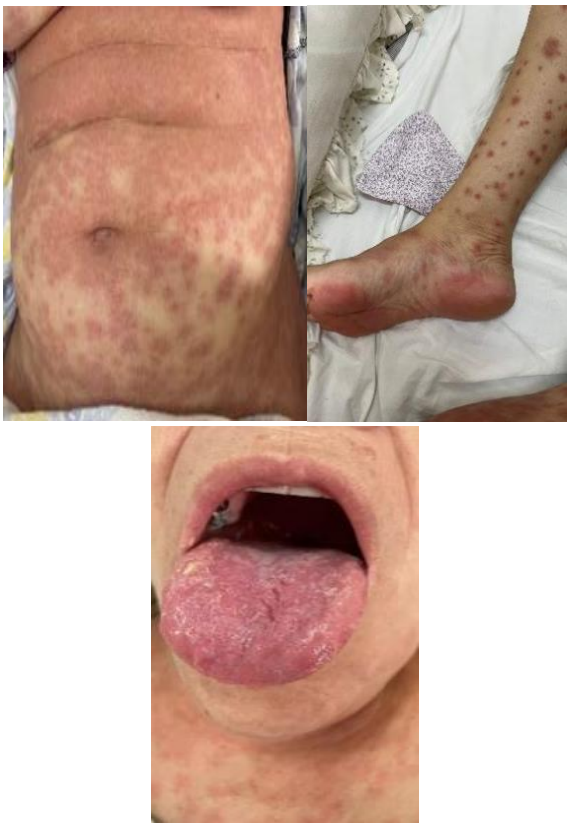

Figure 3. Evolution of pruritic urticarial plaques in different regions of the body after treatment with corticosteroids, recorded on January 3, 2022.

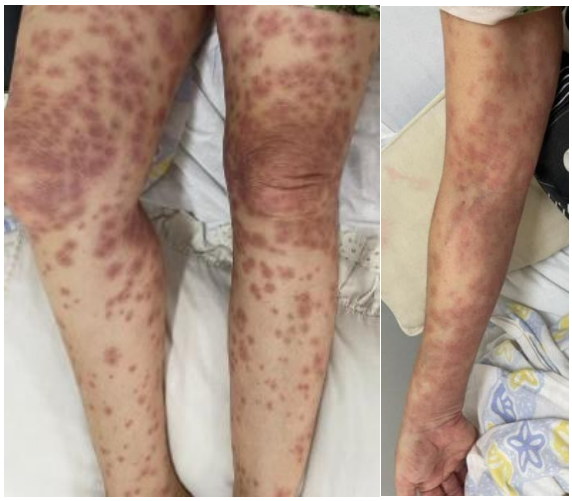

Figure 4. Evolution of pruritic urticarial plaques in different regions of the body after treatment with corticosteroids, recorded on January 4, 2022.

The results of laboratory tests were as follows after seven days of hospitalization: Hb 11.3/ Ht 31.6/ leukocytes 13100 – segmented 9537; lymphocytes 2188; monocytes 1153; eosinophils 131; basophils 92/ platelets 144000/ creatinine 0.84/ urea 25/ Pcr 2.0. The patient was discharged after showing clinical improvement and lesions in remission. Corticosteroid was suspended and prednisone, Hixizine 25 mg 8/8 h, and promethazine 25 mg 8/8 h were prescribed. In addition, the patient was advised against the use of any non-steroidal anti-inflammatory drug.

DISCUSSION

Several factors are responsible for changing the skin's natural composition and causing diseases that attack this system (American Society of Health-System Pharmacists, 2013). Antibiotics (especially penicillin and other β-lactam) – 20.9%, angiotensin-converting enzyme inhibitors (ACEI), insulin, non-steroidal anti-inflammatory drugs (NSAIDs) – 16.7%, diuretics, anticonvulsants, and anesthetics – 13% are the drugs most related to pharmacodermia (Antunes *et al*., 2013). The patient had a diagnosis of asthma – a hypersensitivity disease of the airways – associated with a previous history of allergic reactions to different drug classes, including NSAIDs, and used the anti-inflammatory Flancox (etodolac) for two consecutive days due to low back pain, being one of the medications with risk for the development of pharmacological interaction.

Pharmacodermia occurs by two main mechanisms: the allergic and non-allergic mechanisms. The allergic mechanism follows the Gell-Coombs classification, which divides the mechanism into four categories, namely: immediate (anaphylactic) – Type I, cytotoxic – Type II, immune complexes – Type III, and delayed hypersensitivity – Type IV. Importantly, the allergic mechanism is dose-independent and affects only susceptible individuals, who may develop severe pharmacodermia even at very small doses (Oliveira *et al*., 2019).

Type I occurs by stimulating the degranulation of mast cells produced by the presence of circulating IgE, culminating in the release of histamine. It is represented by urticaria, angioedema, and anaphylactic shock (Bolognia JL *et al*., 2012). Mast cells showed a significant increase as described above in the patient.

Type II occurs through cytotoxic antibodies, with direct cell damage. This group has as an example drug-induced bullous pemphigoid and drug-induced thrombocytopenia such as heparin-induced thrombocytopenia (HIT) (Kennedy & Dixit, 2016).

Type III occurs through the formation of immune complexes, that is, complexes containing antigens and antibodies, generating autoimmune diseases and drug-induced vasculitis (Azulay, 2013).

Finally, type IV is the only one in the classification mediated by cellular immunity, not by humoral immunity, being affected by the action of T lymphocytes. An example is the Steven-Johnson syndrome and toxic epidermal necrolysis (TEN). Types I and II are mediated by antibodies (Type I = IgE and type II = IgM and IgG), while type III is mediated by immune complexes and type IV by cells (T lymphocytes and cellular immunity) (Kennedy & Dixit, 2016).

The non-allergic mechanism is more common than the allergic mechanism. It occurs due to some factors, such as drug overdose (the body cannot metabolize or excrete, generating adverse effects), individual factors (mainly liver and/or kidney pathologies, with changes in drug metabolism and excretion), side effects already known to drugs, and drug use teratogenesis. Moreover, the non-allergic mechanism is dose-dependent and can affect any individual (Fitzpatrick, 2010).

The clinical manifestations of pharmacodermia can be described as exanthemas, urticaria, fixed pigmented erythema, photosensitivity, lichenoid, acneiform, porphyria, pigmentation, and dyschromia conditions, acute generalized exanthematous pustulosis, erythroderma (scaly and exfoliative), vasculitis, and vesico-bullous conditions (Alonzo & Cepeda, 2013).

It is the result of immunological mechanisms called hypersensitivity reactions to drugs when it occurs due to an allergic reaction, not dependent on the dose but on the susceptibility of the individual and may present clinical signs restricted to the skin or in a systemic way (Figueiredo *et al*., 2017). Examples of pharmacodermia by non-allergic mechanisms are skin necrosis caused by coumarins (due to the initial prothrombotic effect of coumarins, leading to thrombosis of superficial skin vessels), Jarisch-Herxheimer reaction (it may be associated with the release of toxic substances by the *Treponema pallidum* killed in the treatment of syphilis with benzathine penicillin, worsening skin lesions), and non-allergic urticaria (the medication itself leads to mast cell degranulation, with the release of histamine; examples: iodinated contrast and morphine).

Special care should be taken when using antihypertensive drugs, especially when the patient used polypharmacy and had numerous comorbidities because the more diseases, the more medications are taken and the higher the probability of causing an adverse reaction.

Therefore, the patient of the report presented a type I pharmacodermia – anaphylactic.

CONCLUSION

Anti-inflammatories were the pharmacological classes with the highest incidence in cases of pharmacodermia. There is an urgent need for results from randomized trials on appropriate prophylaxis and treatment. This class is among the most prescribed in the world daily. Therefore, the need for a multidisciplinary team, the doctor-patient relationship, and the pharmacy are essential for the rapid identification of possible pharmacodermia.

Pharmacodermia has a low incidence but high mortality. Thus, early recognition and withdrawal of the causative drug are essential to the treatment. However, more studies addressing the topic of pharmacodermia should be carried out to improve knowledge in the area of pharmacists and other health professionals.

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