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Clinical Review of the Most Cutaneous Reactions

Daniela Reyes Rojas[1], Frida Yazmin Ayestaran Figueroa[2], Diana Elizabeth Medina Castillo[3]* and Diana Alejandra Aguilar Medina[4]

[1]*First-year Resident in Internal Medicine at General Hospital "Dr. Nicolás San Juan", Mexico.*

[2]*Third-year Resident in Internal Medicine at General Hospital Toluca ISSSTE, State of Mexico.*

[3]*Dermatology, Private Practice at D'Corium Dermatological Private Consultation, Metepec, State of Mexico.*

ORCID ID 0000-0001-5087-5372

[4]*Dermatologist, Cutaneous Surgery and Oncology, Mohs Surgeon at D'Corium Dermatological Private Consultation, Metepec, State of Mexico.*

***Correspondence:**

Diana E. Medina Castillo, Dermatology, private practice at D'Corium Dermatological Private Consultation, Metepec, State of Mexico, Tel:7222130071.

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ABSTRACT

Cutaneous adverse drug reactions (CADRs) are a group of clinical manifestations affecting the skin, mucous membranes, and skin appendages secondary to drug exposure. Cutaneous involvement occurs in up to 45% of adverse drug reactions, of which 10% corresponds to hospitalized patients.

The most common are maculopapular rash, urticaria/angioedema, fixed drug eruption, lichenoid eruptions, and erythema multiforme. Less common but potentially life-threatening dermatoses include erythroderma, serum sickness disease, acute generalized exanthematous pustulosis (AGEP) and symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN).

Any drug can induce a drug-induced skin reaction; the most frequent culprits are antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), antiepileptics.

Drug-induced skin reactions are classified as type A (exacerbation), type B (unpredictable), and by phenotype.
Risk factors include age, as it affects children and the elderly more frequently; female sex; polypharmacy; hospitalization; previous drug eruption; and kidney and liver disease, among others.

The common pathogenesis of severe drug eruptions includes a genetic link with HLA and non-HLA genes, drug-specific T-cell-mediated cytotoxicity, T-cell receptor restriction, and other cytotoxicity mechanisms.

Diagnosis of a drug eruption involves a thorough interview and the timeline of the dermatosis's onset a detailed clinical, morphological, and topographic examination; and staging studies such as laboratory tests and/or skin biopsy.

The treatment should include discontinuation of the suspected medication, and depending on the severity; Immunoglobulin G, topical or systemic corticosteroids, and cyclosporine A.

Keywords

Drug eruption, Drug hypersensitivity syndrome, Drug-induced skin disease.

Introduction

Pharmacodermias also known as drug eruptions or cutaneous adverse drug reactions are a harmful or unwanted effect that affects the skin, mucous membranes, and/or appendages (hair, nails, and

glands), secondary to virtually any medication. The drugs involved include over-the-counter medications, vaccines, natural products, home remedies, and traditional medicine administered through any of the following routes, including oral, injection, inhalation, suppository, infusion, or topical; at prophylactic, diagnostic, or therapeutic doses [1,2].

They are generally divided into two categories: type A pharmacological reactions, which are dose-related, predictable, and determined by the characteristics of the drug, and type B reactions, which are not dose-related, are unpredictable and are related both to the individual's constitution and to the drug itself. According to the literature, adverse drug reactions affect the skin in up to 45% of cases and account for 2% to 5% of dermatoses [3]. Most cutaneous manifestations can disappear with immediate discontinuation of the drug and appropriate treatment. However, severe cutaneous adverse drug reactions not only have a sudden onset or extensive and severe skin lesions, but can also cause symptoms in multiple organs and may be so severe as to result in death [4]. The prevalence of CADRs is 1–3% among adult patients, while around 2.5% of children treated with a medication will experience these reactions. In general, CADRs affect up to 10% of all hospitalized patients. Fortunately, most CADRs are mild conditions or self-limiting; however, between 2% and 6.7% of skin reactions can develop into severe and potentially life-threatening clinical syndromes. These severe cutaneous adverse reactions have an overall frequency of 0.4 to 1.2 cases per million per year, but their incidence varies depending on the population and the triggering drug [5]. Zhang et al. reported that the estimated incidence of CADRs could range from 1 in 1,000 to 1 in 10,000 drug exposures.

Clinically, a drug can induce different dermatological patterns with diverse pathophysiology; however, most of these studies do not include cutaneous adverse reactions associated with drug side effects, including chemotherapy or biological therapies, since they are so numerous and varied that they would be the subject of another publication. The most commonly reported triggering drugs are antiepileptics, antimicrobials, analgesics, anti-inflammatory/antipyretics, antipsychotics, and vaccines [6]. In the FDA Adverse Event Reporting System database, 77,789 reports related to severe cutaneous adverse reactions (SCAR) were considered, of which lamotrigine (6.2%) was the most reported drug, followed by paracetamol (5.8%) and allopurinol (5.8%). Antibiotics (20.6%) were the most reported drug class, followed by antiepileptics (16.7%) and oncological drugs (11.3%) [7].

Risk Factors

In general, anyone could develop a CADR; however, there are risk factors associated with these conditions such as:

1. Female sex has been associated with a higher risk of abuse of medications. Compared to men, women have lower body weight and organ size, a higher amount of body fat, different gastric motility, and a lower glomerular filtration rate. These differences can affect how the body processes drugs, altering pharmacokinetics and pharmacodynamics, including absorption, distribution, metabolism, and elimination.
2. Age at the extremes of life is more frequent; for example, neonates whose storage, metabolism, or receptor systems are still immature and may also have failures in their elimination systems. In patients older than 60 years, this can be attributed to the senescence of these systems, in addition to having comorbidities that make them prone to having multiple treatments (polypharmacy).
3. Hospitalized patients have up to 10 times higher risk of suffering from drug-induced skin reactions, since during the hospital stay multiple drugs are used according to the condition and its progression.
4. Viral infections may predispose or exacerbate drug-induced skin reactions due to states of immune imbalance, making the host more susceptible to presenting cutaneous disease due to drugs.
5. Patients who have a history of previously having suffered a drug eruption have an increased risk of presenting another one, since they may be chemically similar or the patient may have genetic conditions of inadequate drug metabolism.
6. Patients with hepatic insufficiency due to disorders in the distribution, storage, and metabolism of the drug, and nephropathic patients due to deficient excretion of drugs.
7. Patients with chronic diseases and polypharmacy such as rheumatoid arthritis, diabetes mellitus, chronic kidney disease, acquired immunodeficiency syndrome (AIDS), among others [8].
8. The risk of developing a CADR increases with the number of genetic variations in drug metabolism and the association of human leukocyte antigens (HLA). For example, several authors have described genetic associations between specific HLAs and an increased risk of developing CADR in specific populations such as:
    a. HLA-A*31 and carbamazepine.
    b. DRESS induced in the North African population.
    c. HLA-B*58:01 and DRESS
    d. SJS/TEN in East Asians treated with allopurinol [9].

More than 35 clinical presentations of drug eruptions are known. There are several ways to classify these conditions by their morphology, time of onset, severity, pathophysiology, or the classic ADR classification described by Rawlins and Thompson in 1977 (type A, B). Predictable or type A reactions occur due to the action of the drug through the same mechanisms by which it exerts its therapeutic effect. They are the most frequent (85 to 90% of drug-induced dermatoses) and may be related to the drug dose; therefore, they are usually predictable and are part of side effects and interactions with other drugs.

Unpredictable or type B reactions are triggered by enzymopathies, cytokine imbalances or inflammatory mediators, non-specific mast cell degranulation, and various hypersensitivity mechanisms. Among the latter, the most frequent are those mediated by IgE (type I) or by T cells (type IV); or those that can be explained by the hapten/pro-hapten concept and/or by the direct interaction of drugs with immunological receptors (P-i concept). They account

for approximately 10 to 15% of drug-induced dermatoses. They are usually not related to the drug dose, depend on the patient's susceptibility and therefore cannot be predicted [10].

Classification

CADRs can also be classified according to their clinical appearance. A recent classification divides CADRs into 4 main categories:

i. Exanthematous
ii. Urticarial
iii. Bullous
iv. Pustular

However, some morphological patterns do not belong in these four categories, so they can be placed in a miscellaneous group. On the other hand, they are also subclassified as simple (mild) or complex (severe) according to their topography and morphology. Simple cutaneous drug reactions are primarily limited to the skin and/or mucous membranes without systemic involvement, whereas complex ones are accompanied by systemic signs such as fever, general malaise, hypotension, tachycardia, lymphadenopathy, reactive arthritis, respiratory failure, hepatic, renal, or cardiovascular involvement, which could put the patient's life at risk. Within this latter group are SJS, TEN, DRESS, and AGEP, which are the most recognized; however, other conditions such as drug-induced pemphigus and linear IgA disease are not excluded, as they can also present with systemic involvement and may require or prolong the patient's hospitalization [11].

Diagnosis

The clinical presentation and their chronology, that is, the time of drug exposure and the time of appearance of the dermatosis, will be described in each type of drug eruption.

Anamnesis

According to the German guidelines for determining drug hypersensitivity, consensus drafted in 2023 [12], the following aspects should be carried out during the clinical history:

1. Identification of the organs involved in the drug reaction, including those affecting the skin, mucosa, respiratory and gastrointestinal systems, liver, and kidney.
2. Description of the topography and clinical morphology of cutaneous or mucosal manifestations; if clinical photographs are available, they provide valuable documentation.
3. Accompanying symptoms such as fever, hypothermia, or general malaise.
4. Observe the course of the disease and whether there are morphological changes over the time, reclassify the reaction.
5. Laboratory findings, such as eosinophilia, thrombocytopenia, alterations in nitrogenous waste (urea and creatinine), serum tryptase levels, etc.
6. Histopathological findings using routine staining, especially in drug eruptions with bullous presentation (the immunofluorescence will be necessary to determine the type of dermatosis we are dealing with)
7. Determine phenomena concurrent with drug-induced dermatosis, that is, whether concomitant with the presentation of the reaction there is a viral infection (e.g., infectious mononucleosis and amoxicillin), if the patient also consumed any food (example: the case of antihistamines and fruit juices), if they are under stress, alcohol intake (e.g., metronidazole and alcohol, antabuse effect), sun exposure (photoallergy and intake of nonsteroidal anti-inflammatory drugs), and menstruation (appearance of fixed pigmented erythema after the intake of mefenamic acid to reduce premenstrual pain).
8. Verify the drug used, indication, brand or active name to avoid confusion between medication names (e.g., dicloxacillin–doxycycline), investigate reactions similar to the one presented by the patient with medications (e.g., latex allergy), do not forget to ask if the patient has prior diseases such as atopic dermatitis, chronic urticaria, mastocytosis, rhinitis, asthma, polyposis. Ask about mental illnesses or somatization, habits in the patient such as smoking, alcohol intake and drugs; finally, ask about chronic diseases and their treatments to rule out drug interactions.
9. Corroborate the chronology of the drug-induced dermatosis with the timing of drug administration; ask whether this is the first time it has occurred, what therapeutic measures were taken, the clinical course and resolution of the dermatosis.
10. Clinically classify the dermatosis, including accompanying symptoms and the time at which the reaction occurred.
11. It is necessary to specify whether the reaction was caused by a single medication or by multiple medications.

Diagnostic Tests To Detect Drug Hypersensitivity

These are indicated to identify prior sensitization and to explore the immunological mechanisms involved in drug reactions.

Epicutaneous tests are used to detect pharmacological reactions due to type IV hypersensitivity. They mainly study penicillin derivatives, cephalosporins, quinolones, macrolides, anticonvulsants, nonsteroidal anti-inflammatory drugs, antihypertensives, and antivirals. The company Chemotechnique offers 31 allergens available in its Cutaneous Adverse Drugs Series CAD1000.

In a Tunisian cohort, patients with severe CADRs (DRESS, SJS, AGEP) were studied, finding 190 patients over a period of 20 years using epicutaneous tests and oral provocation tests, obtaining a positivity rate of 97.2% for the responsible allergen. This confirmed the diversity of chronological, clinical, and biological patterns of severe CADRs. The present study demonstrated the potential safety and usefulness of skin tests performed at least 6 weeks after resolution of the drug-induced dermatosis to identify the causative drug, evaluate cross-reactivity and co-sensitization, and guide the safe reintroduction of essential therapies. Each hospital center could adopt this study model and adapt it according to the local population, considering the genetic (HLA) factors and the mechanisms of disease production, in order to identify the causative medications [13].

It has been documented that, up to 2023, in Germany only two substances have been approved for the diagnosis of allergy to

benzathine penicillin and procaine penicillin G; these tests are benzylpenicilloyl and benzylpenilloate in solution.

On the other hand, the European Working Group for the study of Drug Allergy (European Network on Drug Allergy ENDA) has specific guidelines and methods for provocation tests that can be performed in a hospital setting. Another group of drugs that are difficult to test are muscle relaxants and narcotics, for which only in vitro studies are available [14,15].

Clinical Picture

The following section describes the most frequent drug eruptions, highlighting their clinical presentation and providing photographic examples of them.

Maculopapular Exanthems

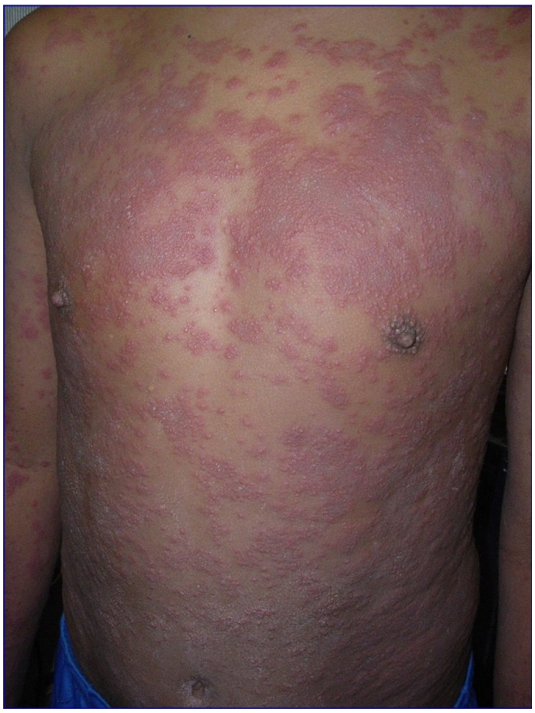

Figure 1: Morbilliform papular exanthem in a patient with infectious mononucleosis after Amoxicillin exposure.

This is one of the most common presentations of drug-induced skin disease and is characterized by small, diffuse macules and papules, pink to red in color, that merge into patches and plaques which initially affect the trunk and then rapidly spread to the proximal and sometimes distal extremities with a symmetrical distribution. They are called morbilliform or measles-like eruptions, scarlatiniform resembling scarlet fever (Figure 1), and rubelliform or like rubella. Drugs often associated with morbilliform reactions include antibiotics (the most common), antiepileptics, and NSAIDs. Exanthems usually appear within the first weeks of exposure—4 to 21 days—to a new drug. In some patients, however, skin manifestations developed months or even years after using the same medication without previous complications [16]. Morbilliform drug reactions do not present with blisters or skin peeling, and enanthem rarely occurs, so it is necessary to rule out viral diseases in the pediatric age group [17]. Other accompanying features include low-grade fever and pruritus of variable intensity, although the rash is reported to be more sensitive or painful. Typically, the skin rash increases after withdrawal of the drug and subsides after 1–2 weeks without leaving sequelae, although post-inflammatory desquamation may occur in rare cases [18].

Fixed Drug Eruption

Fixed drug eruption (FDE) is one of the most characteristic and frequent cutaneous adverse drug reactions. It presents as round or oval, well-defined, erythematous or violaceous lesions that evolve into grayish or brownish tones. These lesions reappear at the same cutaneous or mucosal site if there is re-exposure to the same drug that caused it, or multiple lesions may develop, which is referred to as multifocal. The spots measure between 1 and 10 cm in diameter and may present a central blister (Figure 2), they may leave as a sequela a persistent residual hyperpigmentation, which constitutes the most distinctive clinical hallmark of this condition. The most affected sites are lips, genitals, trunk, and extremities. Mucosal involvement occurs in approximately 20–50% of cases. The latency period after re-exposure to the drug is short [19].

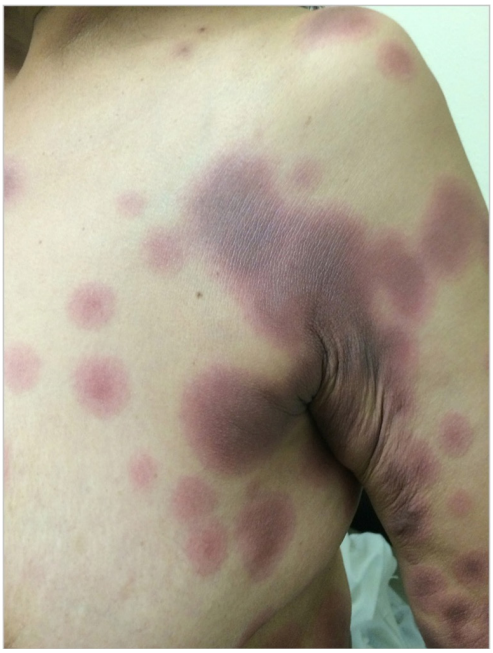

Figure 2: Acute multifocal fixed pigmented erythema due to Trimethoprim/Sulfamethoxazole.

The drugs most frequently involved are NSAIDs, sulfonamides, tetracyclines, fluoroquinolones, and metronidazole [20]. The pathogenesis is due to the presence of CD8+ T lymphocytes residing in the epidermis (tissue-resident memory T cells) that, upon re-exposure to the drug, release granzyme B, perforin, and interferon gamma, causing localized keratinocyte apoptosis. In dark skin, the lesions and residual hyperpigmentation are both are

more evident; this may persist for months or years and responds partially to photoprotection, hydroquinone, or Q-switched laser [21].

Diagnosis is mainly clinical, based on the history of recurrence at the same site and the temporal relationship with the drug intake. When a skin biopsy is performed, it shows basal vacuolization, keratinocyte apoptosis, and a lichenoid inflammatory infiltrate with dermal melanophages [22].

Management consists of immediately discontinuing the causative drug and avoiding re-exposure. High-potency topical corticosteroids can be used. In generalized or bullous forms, systemic corticosteroids or cyclosporine are indicated. The prognosis is generally favorable.

Lichenoid Drug Eruptions

Lichenoid drug eruptions (LDE), account for 2–3% of all drug-induced skin reactions and have been increasing in frequency with the use of immunotherapy and biological drugs [23]. They are characterized by erythematous-violaceous, polygonal, flat, shiny papules with Wickham striae, which tend to coalesce into more widespread and scaly plaques compared to those seen in idiopathic lichen planus. Regarding pathogenesis, cytotoxic CD8+ T lymphocytes are involved by recognizing altered antigens in keratinocytes, with increased interferon gamma production and a greater presence of eosinophils in the lichenoid infiltrate [24]. The eruption predominantly affects the trunk and extensor surfaces, with less involvement of mucous membranes. The latency period is usually prolonged and may last from weeks to months (average of 2–4 months).

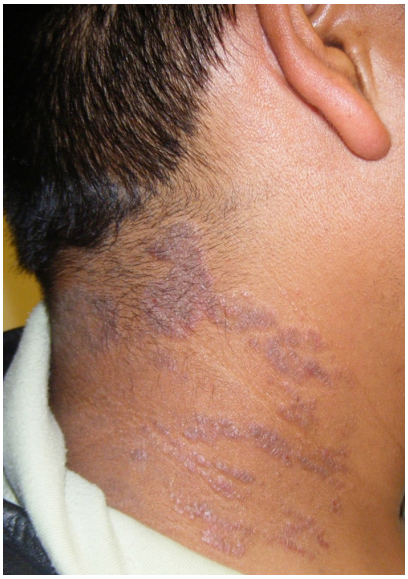

Figure 3: Acute lichenoid eruption due to Quetiapine.

The drugs most frequently associated are antihypertensives (angiotensin-converting enzyme inhibitors, beta-blockers, and thiazides), metformin, antipsychotics (Figure 3), antituberculous drugs, immune checkpoint inhibitors, and tyrosine kinase inhibitors [25]. Diagnosis is based on clinical and histopathological findings. Biopsy shows hyperkeratosis, irregular acanthosis, band-like lichenoid infiltrate, vacuolization of the basal layer, and a greater number of eosinophils compared to classic lichen planus [26].

The treatment consists of immediate discontinuation of the causative drug. Topical corticosteroids of appropriate potency are used, depending on the affected area; in extensive or severe cases, systemic corticosteroids, phototherapy, or JAK inhibitors may be required. Clinical remission is usually slow (3–6 months) and may leave residual hyperpigmentation. The prognosis is favorable.

Syndrome Drug-Related Intertriginous And Flexural Erythema (SDRIFE)

Characterized by an erythematous and pruritic eruption localized mainly to flexural skin surfaces, such as the buttocks and/or the groin. These lesions are well demarcated and may be associated with eczema, erythema, or scaling of the affected areas. The drugs most associated with this condition are penicillins and cephalosporins (Figure 4); however, several other drugs have been implicated, such as clindamycin, erythromycin, nystatin, fluconazole, metronidazole, and valacyclovir. The precise pathogenic mechanism underlying SDRIFE is still unclear; however, it is believed to involve a type IV delayed hypersensitivity immune response supported by immunohistochemical evidence of CD4+ T-cell infiltration. It is considered a self-limited condition without systemic involvement.

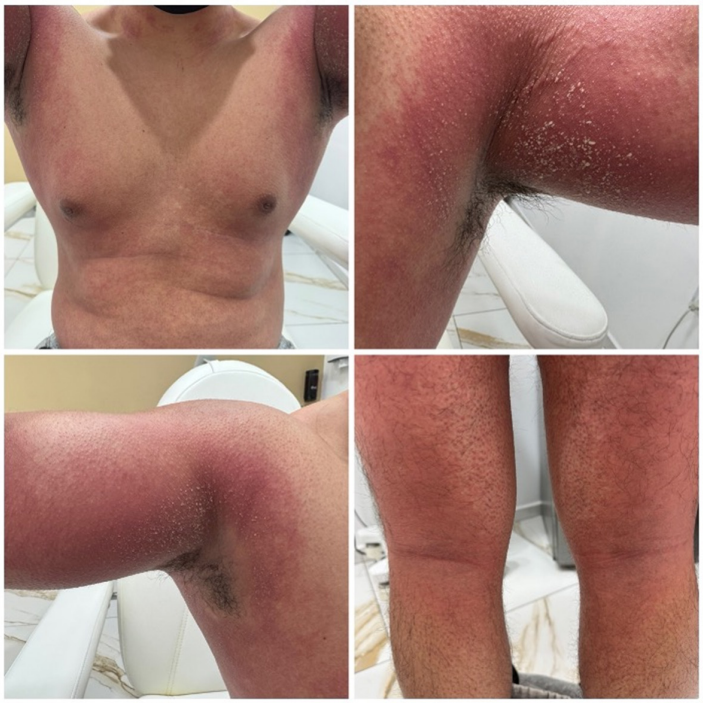

Figure 4: Symmetrical drug-related intertriginous and flexural erythema (SDRIFE) associated to Amoxicillin with clavulanate.

Arias-Rodríguez et al. suggest making a differential diagnosis with Baboon syndrome or mandrill syndrome, since although it is also a type IV delayed hypersensitivity reaction and considered a

systemic contact dermatitis, it is more related to mercury, nickel, and ampicillin in some cases. It is more common in pediatric patients and presents with febrile syndrome [27].

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

DRESS syndrome, previously known as anticonvulsant-induced hypersensitivity syndrome, is a severe cutaneous adverse reaction. The average time to develop symptoms after drug exposure is between 3 and 9 weeks. More than 44 drugs have been identified as involved in the onset of this syndrome, mainly including aromatic amine anticonvulsants, β-lactam antibiotics, and sulfonamides, allopurinol, NSAIDs, and antiretrovirals. In addition, coincident viral reactivation of human herpesvirus 6, other viruses of the human herpesvirus family, CMV and EBV, and an ethnic predisposition associated with a specific human leukocyte antigen (HLA) allele such as HLA-A*31:01, HLA-DRB1*01:01, and HLA-B *35:05 appear to play an important role in the pathogenesis of this condition. Clinically, it begins with fever >38–40ºC, followed by a pruritic exanthem that is often described as diffuse erythematous macular or maculopapular eruption, which may become violaceous. The skin rash is usually accompanied by facial edema. A less common presentation includes other cutaneous morphologies such as pustules, blisters, lichenoid, eczematous, and exfoliative lesions (Figure 5). Patients generally present with palpable lymphadenopathy and involvement of internal organs such as the liver, followed by the kidneys and lungs, while the heart, gastrointestinal tract, and central nervous system are involved less frequently; cases of meningitis and encephalitis have been reported. Laboratory abnormalities include leukocytosis with peripheral eosinophilia, atypical lymphocytes, thrombocytopenia, and abnormal liver and renal function tests. Although eosinophilia is a hallmark of DRESS, this feature may be absent or delayed after liver enzyme elevation returns to normal; mucous membranes are occasionally affected. Patients who recover from this drug eruption have a high risk of developing autoimmune diseases such as Graves' disease, Hashimoto's thyroiditis, type I diabetes, and hemolytic anemia, so long-term follow-up is recommended [28].

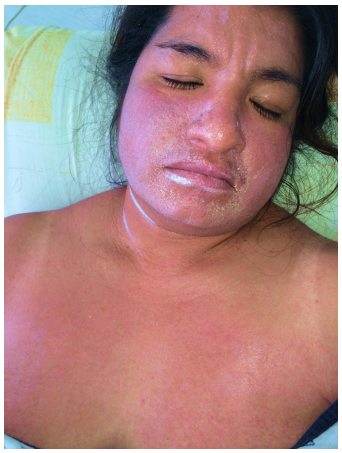

Figure 5: Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) secondary to Azulfidine.

Urticaria and Urticarial Reactions

Urticaria is a condition characterized by the development of wheals that may affect any area of the body and may occur with or without angioedema; Three important characteristics define urticaria (HPP swelling, itching, transient): edema and erythema, a sensation of intense pruritus, and a transient nature course. Individual lesions generally resolve between 30 minutes and 24 hours without leaving residual hyperpigmentation.

Urticaria results from the release of inflammatory mediators from mast cells and basophils, through either immune mechanisms such as type I hypersensitivity reaction (e.g., IgE-mediated) and non-immune mechanisms (direct mast cell degranulation by NSAIDs). Urticaria or urticarial lesions may initially be solitary or multiple; their size varies from a few millimeters to several centimeters. The morphology includes annular, pseudoannular (incomplete rings) or polycyclic patterns. Its course is dynamic as lesions may fade and reappear in different areas of the body (Figure 6). The most common drugs associated with this presentation include NSAIDs, sulfonamides, phenytoin, morphine, codeine, penicillin, and cephalosporins. Oral antihistamines are often useful in reducing pruritus and the appearance of lesions. Anaphylaxis is an acute reaction characterized by hypotension, bronchospasm, or gastrointestinal symptoms accompanied by urticaria/angioedema; patients should be instructed to seek emergency service as this is a potentially life-threatening manifestation [29,30].

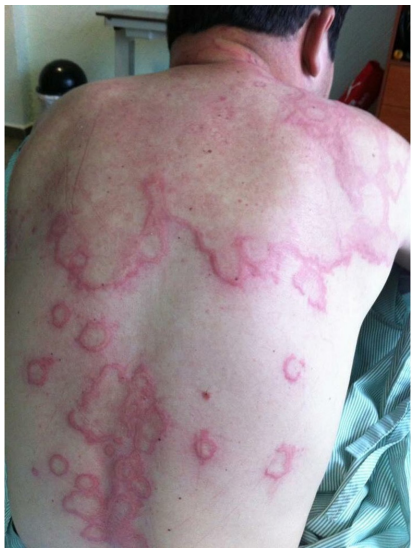

Figure 6: Acute annular urticaria due to Cefuroxime.

Serum Sickness

Serum sickness is a type III hypersensitivity reaction mediated by immune complexes, accompanied by fever, urticarial eruptions occasionally macular or vasculitic with arthralgias, rarely arthritis. There are other less common symptoms such as headache, neuropathic pain, lymphadenopathy (Figure 7). Laboratory tests show hypocomplementemia in CH50, C3 and C4; there may be an increase or decrease in leukocytes and elevated serum creatinine. There is another reaction like serum sickness (Serum sickness-like reaction), except that the clinical manifestations are more severe,

including eyelid and lip edema, which has been associated with beta-lactam antibiotics and cephalosporin rings; it is suggested that the pathophysiology is thought to correspond more closely to a delayed type IV hypersensitivity [31,32].

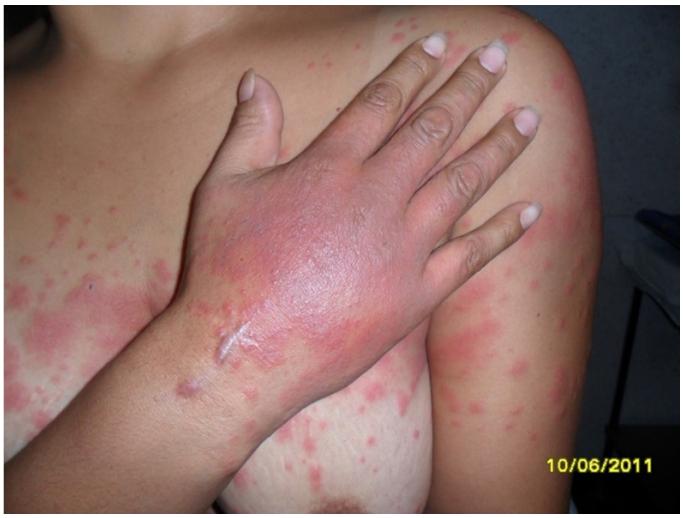

Figure 7: Serum sickness after vaccination against Influenza A H1N1.

Erythroderma or Generalized Exfoliative Dermatitis

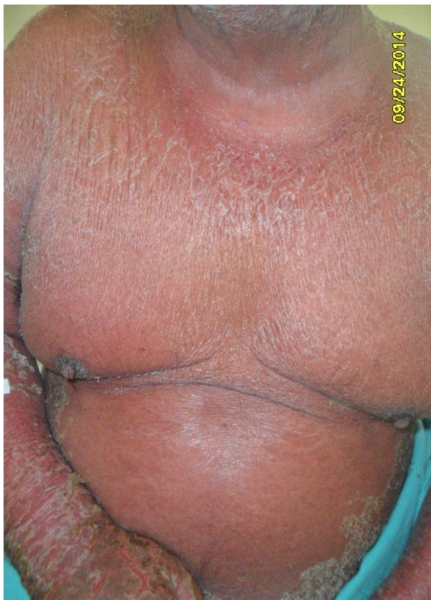

Figure 8: Erythroderma due to Carbamazepine as treatment for post-herpetic neuralgia.

Erythroderma is clinically defined as generalized erythema with scaling involving more than 85% of the body surface area; it is severe and potentially life-threatening. Drug-induced erythroderma represents the second most common cause of erythroderma, ranging between 11.3% and 21.6% of cases. The list of drugs causing erythroderma is extensive; anticonvulsants such as carbamazepine and uricosurics such as allopurinol stand out as the medications with the greatest capacity to trigger erythroderma. Possible causes include genetic susceptibility or the frequency of prescription. In HIV-seropositive patients, antituberculosis drugs are implicated. Other drugs associated with this condition include phenytoin, beta-lactams, sulfonamides, phenobarbital, sulfasalazine, omeprazole, traditional Chinese herbal products, and non-ionic contrast media. Erythroderma develops gradually and insidiously, except in cases of drug origin. The skin usually appears bright red, dry, warm, and indurated. Most patients complain of pain or pruritus (Figure 8). In drug-induced forms, the scales are small and pityriasiform. Hyperpigmentation or hypopigmentation may also occur. The nails may become thickened, dry, brittle, shiny, and ridged [33].

Acute Generalized Exanthematous Pustulosis (AGEP)

Acute generalized exanthematous pustulosis is a severe cutaneous adverse drug reaction, characterized by the sudden appearance of multiple sterile, non-follicular pustules on a diffuse erythematous base. It is considered an uncommon drug eruption, but clinically relevant within the category of severe cutaneous adverse drug reactions (Figure 8) [34].

Most of these cases are associated with recent exposure to medications, with antibiotics (beta-lactams and macrolides), antifungals, calcium channel blockers, and antimalarials leading the list. The latency period is generally short, between 24–48 hours in previously sensitized patients, which constitutes a key element for clinical diagnosis [35]. AGEP corresponds to a type IVd delayed hypersensitivity reaction, mediated by drug-specific T cells. These cells induce the release of proinflammatory cytokines, specifically interleukins 8, 17, and GM-CSF, which promotes massive recruitment of neutrophils to the epidermis and the formation of pustules characteristic of this type of reaction. The inflammatory cascade is also associated with epidermal damaged keratinocytes apoptosis [36].

It is characterized by the acute appearance of millimetric, superficial, non-follicular pustules on an erythematous base that usually begins on the face or folds and rapidly spreads to the trunk and extremities (Figure 9). It is also associated with fever and asthenia and leukocytosis with neutrophilia, which may simulate an infectious process. In this case, mucosal involvement is infrequent or mild compared with other severe drug eruptions [37]. Diagnosis is purely clinical, based on the temporal relationship with drug exposure and the morphological characteristics of the lesions. In some cases, a skin biopsy may show subcorneal or intraepidermal pustules with neutrophilic infiltrate and superficial dermal edema [38].

Management consists of immediately discontinuing the suspected drug and providing supportive measures such as hydration, with intravenous fluids if necessary, and monitoring renal function and electrolytes (sodium-potassium), analgesia, and avoiding NSAIDs if they are related to the trigger. In most cases, the course is self-limited and resolves within 1 to 2 weeks, leaving characteristic superficial desquamation and with a generally favorable prognosis compared to other severe cutaneous reactions

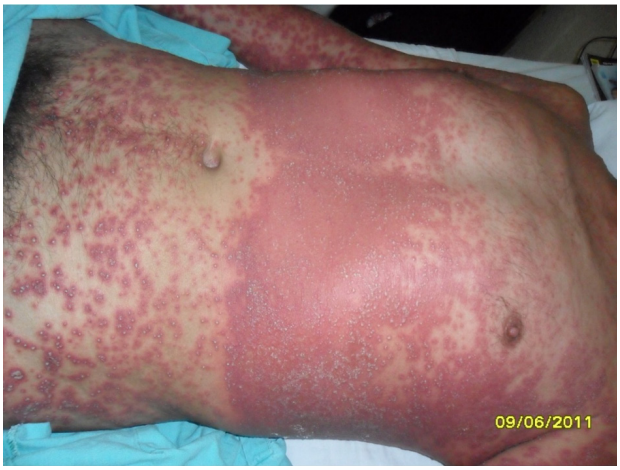

Figure 9: AGEP Acute Generalized Exanthematous Pustulosis due to Cefadroxil.

Erythema Multiforme (Em) Due To Drugs

Erythema multiforme is an acute mucocutaneous reaction characterized by the appearance of target lesions (target lesions) (Figure 10), which are characteristic and represent a hypersensitivity response mediated by immunological mechanisms. Although it is classically associated with infections, generally due to the herpes simplex virus [39] and Mycoplasma pneumoniae, in a smaller proportion it is related to drug exposure (<10%), which is why it is considered predominantly infectious. The medications most frequently associated are antibiotics (sulfonamides, penicillins, and cephalosporins), NSAIDs, and anticonvulsants. Unlike other severe drug reactions, the latency period can vary from days to weeks after the initial exposure to the drug and depends on the degree of patient sensitization [40].

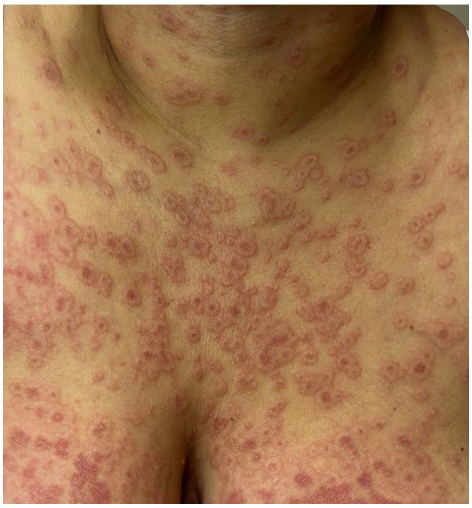

Figure 10: Erythema multiforme due to Ampicillin.

Drug-induced EM corresponds to a delayed type IV hypersensitivity reaction mediated by T lymphocytes and CD8+ cytotoxic cells. These lymphocytes recognize antigens derived from the drug or metabolites expressed in keratinocytes, which induces localized cellular apoptosis through mechanisms such as the release of perforins, granzymes, and Fas-FasL interaction. This process causes focal epidermal damage and the formation of the typical target lesions [41].

It presents with typical target-shaped skin lesions as previously mentioned, which are composed of three concentric zones: a necrotic or vesicular center, a pale halo, and a peripheral erythematous ring. These lesions predominantly appear on the extensor surfaces of the extremities, particularly on the hands and feet, with symmetrical distribution. It is classified into minor and major EM. When there is limited skin involvement without significant mucosal involvement, it corresponds to the former, and when there is involvement of one or more mucous membranes, generally oral, ocular, or genital, it corresponds to the latter and is usually differentiated from Stevens-Johnson syndrome; however, the latter is associated with drugs and erythema multiforme major with herpes simplex virus [42].

Diagnosis is clinical, based on the morphology of the lesions and the temporal relationship with drug exposure. In atypical cases, skin biopsy may show interface dermatitis with keratinocyte necrosis and a perivascular lymphocytic infiltrate. Discontinuation of the triggering drug is the initial management along with supportive measures. In most cases, the course is self-limited with resolution in 1–3 weeks, and symptomatic treatment includes antihistamines such as loratadine or cetirizine and topical corticosteroids. In cases of significant mucosal involvement or extensive disease, systemic corticosteroids may be considered. The prognosis is usually favorable, with low mortality [43].

Stevens-Johnson Syndrome

Stevens-Johnson syndrome (SJS) is a severe, potentially life-threatening adverse skin reaction characterized by extensive epidermal necrosis and mucocutaneous involvement. It is part of a spectrum along with toxic epidermal necrolysis (TEN), differing mainly by the extent of body surface area affected, which is less than 10% in SJS [44]. In most cases, SJS is associated with drug exposure, with the most frequently implicated being allopurinol, anticonvulsants (carbamazepine, phenytoin, lamotrigine), antibiotics (sulfonamides, beta-lactams), and nonsteroidal anti-inflammatory drugs. The latency period is 1–3 weeks after drug exposure [45].

It is a delayed hypersensitivity reaction mediated by cytotoxic CD8+ T lymphocytes and NK cells. These two types of cells release cytotoxic mediators, leading to massive apoptosis of keratinocytes. Although mechanisms such as the release of perforins, granzymes, and activation of the Fas-FasL pathway are also present in erythema multiforme, the damage there is limited and localized. In SJS and toxic epidermal necrolysis, the damage is more intense and widespread and is characterized by a predominant release of granulysin, which is directly associated with massive keratinocyte apoptosis and extensive epidermal necrosis [46].

It begins with a nonspecific prodrome characterized by fever, general malaise, odynophagia, and upper respiratory symptoms. Following this, erythematous or maculopapular skin lesions appear, which evolve into blisters and areas of absence of epidermis with a positive Nikolsky sign. In this case (Figure 11), mucosal involvement is a fundamental characteristic and is present in more than 90% of cases [47].

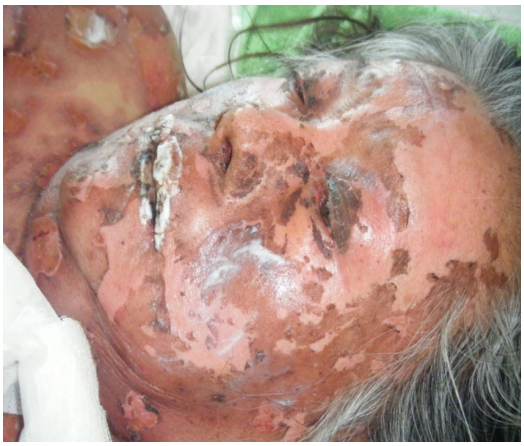

Figure 11: SJS Stevens-Johnson Syndrome due to Allopurinol.

The diagnosis is clinical and is based on the morphology of the lesions. It also presents with target lesions that evolve into vesicles with skin detachment or a positive Nikolsky sign, indistinguishable from blistering diseases such as pemphigus; however, the onset with target-like lesions supports the diagnosis of SJS, along with mucosal involvement and the temporal relationship with drug exposure. A biopsy of the affected tissue can confirm the diagnosis by demonstrating complete epidermal necrosis with minimal inflammatory infiltrate. Treatment requires hospitalization and immediate discontinuation of the causative drug. Supportive care should be provided, including fluid management and correction of hydroelectrolytic imbalances, pain management, care of the affected skin, and prevention of secondary infections. The prognosis depends on the extent of skin involvement and the patient's general condition, with an approximate mortality of 5–10% [48].

Toxic Epidermal Necrolysis Syndrome or Ten

Toxic epidermal necrolysis (TEN) is characterized by being potentially life-threatening and by extensive epidermal necrosis, with skin detachment involving more than 30% of the body surface area. It differs from Stevens-Johnson Syndrome mainly by the extent of skin involvement and clinical severity [49]. It is mainly associated with exposure to drugs such as allopurinol, anticonvulsants, and antibiotics (beta-lactams and sulfonamides); the latency period ranges from 1–3 weeks after initial exposure [50].

Clinically, it presents with a prodrome similar to that of SJS, with fever, asthenia, and upper respiratory symptoms, followed by the appearance of erythematous skin lesions that rapidly evolve into blisters and extensive areas of epidermal detachment, with a positive Nikolsky sign. Mucosal involvement is constant and severe, affecting the oral, ocular, and genital cavities, which directly impacts patient morbidity (Figure 12) [51].

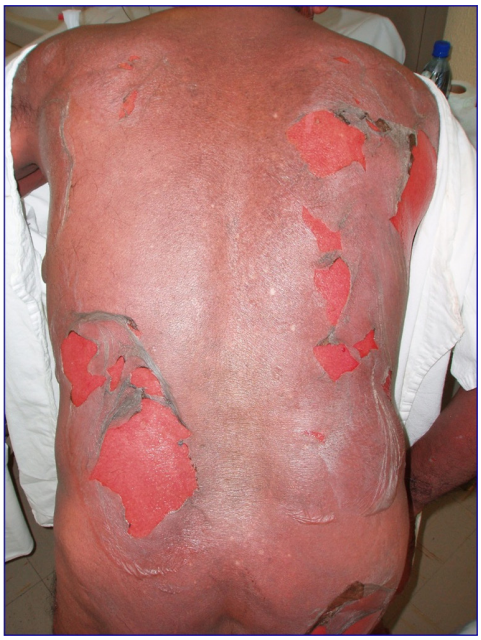

Figure 12: TEN Toxic Epidermal Necrolysis due to Metamizole.

The diagnosis is clinical, based on the extent of skin detachment and the history of drug exposure; a skin biopsy confirms the diagnosis by demonstrating complete epidermal necrosis. It is essential to differentiate it from other blistering dermatoses and from SJS, since TEN has higher mortality and generally requires management in intensive care or burn units, as well as a multidisciplinary approach, given that the loss of skin integrity leads to fluid and electrolyte loss and infections. The pathophysiology is similar to that of an extensive burn. The cornerstone of treatment remains the immediate discontinuation of the offending drug, followed by supportive measures; in this case, early enteral nutritional support is essential to reduce catabolism and promote tissue regeneration [52]. The use of systemic immunomodulatory therapies is controversial; however, cyclosporine in early stages has shown benefits by inhibiting T-lymphocyte activation and reducing the progression of necrosis. The use of steroids has been employed in these cases but remains a topic of debate due to the possible risk of infections. Biological therapies such as etanercept (a TNF-α inhibitor) have also been explored, with promising results in recent studies. Prognosis is assessed using the SCORTEN scale, which estimates mortality based on clinical and biochemical variables. Mortality remains high despite therapeutic advances, highlighting the importance of timely diagnosis [53].

Final Comments

It is very important to clinically identify and classify drug eruptions. A good medical history will reveal the risk factors for developing the eruption.

With this review, we aim to ensure that any physician, not just a dermatologist, can recognize the type of dermatosis they are facing and know how to manage it to avoid complications.

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