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Review Article

Severe Cutaneous Adverse Drug Reactions: From Causes to Mechanisms

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Amelia Morgillo[1,2], Edoardo Marovino[3], Marcello Mazzarella[4], Valerio Barbagiovanni[4], Maria Francesca Randazzo[5]

1. University of Siena, Italy; 2. Department of Medicine and surgery, Saint Camillus International University of Health Sciences, Rome, Italy; 3. University of Milan, Italy; 4. Saint Camillus International University of Health Sciences, Rome, Italy; 5. University of Turin, Italy

Introduction: In the context of adverse drug reactions (ADR), skin manifestations are among the most frequent and often of such severity as to require access to the emergency room for emergency injection therapy. In this article, we wanted to describe the characteristics of severe skin reactions both from a clinical point of view and with regard to the mechanisms and drugs most often involved in the cause.

Methods: Both the use of personal paper books and international website databases such as PubMed, Scopus, Google Scholar, and ResearchGate were used to develop the article, typing in keywords such as "skin ADR," "severe drug reactions," "Lyell or Steven-Johnson syndrome," associated with specific compound names. We have focused on recent articles and only those related to severe ADRs.

Results and Conclusions: With regard to cutaneous ADRs, mild or moderate presentations can be distinguished, such as morbilliform or scarlet eruptions with or without systemic symptoms, which are fortunately more frequent and generally treatable through the use of partially injected drugs and with oral therapy, and which self-resolve in a few days. Up to severe and potentially fatal erythrodermal forms such as DRESS or Stevens-Johnson and Lyell's syndromes, two different phases of the same process, with dermatological pictures similar to burns. Lists of higher-risk drugs have been established, and every physician, including general practitioners, should know their potential for toxicity before prescribing and the need for closer clinical monitoring. Pay attention to the differential diagnosis with infectious processes, sometimes concomitant, and to primary forms of dermatosis such as severe forms of psoriasis or acne.

Corresponding author: Amelia Morgillo, dr.ameliamorgillo@gmail.com

Introduction

Drugs play an essential role in the treatment and prevention of many diseases, and this is demonstrated by the enormous expansion of the pharmaceutical market from 2000 to today; however, no drug is free

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from side effects (sometimes even serious), and their use can be related to both the risk of ineffectiveness and poisoning from excessive doses. The definition of adverse drug reactions (ADR) has undergone changes in recent years.[1]

A first definition was developed about thirty years ago by the WHO, which defined it as *"a response to a drug that is harmful and unintentional and that occurs at doses that are normally used in humans for the prophylaxis, diagnosis or therapy of a disease or that arises as a result of changes in the physiological state "*[2]. Today, the new legislation on pharmacovigilance has changed the definition of adverse reaction, now understood as *"any harmful and unwanted effect resulting from the use of a medicine"*[3][4]. The task of pharmacovigilance is to provide, on an ongoing basis, the best possible information on the safety of drugs, thus allowing appropriate measures to be taken and therefore ensuring that the drugs available on the market present, under the authorized conditions of use, a beneficial relationship. favorable risk for the population"[5][6]. In 2002, it was defined by the World Health Organization (WHO) as "the science and activities related to the identification, evaluation, understanding and prevention of adverse reactions or other drug-related problems".[7] The concept of ADR is part of the more general concept of "adverse event", defined as "any unwanted medical event, which arises in a patient (or in a subject included in a clinical study) who is administered a drug and who does not necessarily have a causal relationship with the treatment".[8] This definition, therefore, as can be understood, includes a wide variety of events that may arise during drug therapy, such as adverse drug reactions, therapeutic failure, and overdose. They are included in the ADR:

- Use not in accordance with the instructions contained in the marketing authorization (off-label)
- Medication errors, including accidental overdose
- Improper use
- Abuse of the drug
- Association to the exhibition for professional reasons

COLLATERAL EFFECT	any unintended effect of a drug arising at the doses normally used in humans and related to its pharmacological properties
ADVERSE EVENT	any unpleasant clinical phenomenon that occurs during a drug treatment but which does not necessarily have a causal relationship with the drug itself
ADVERSE DRUG REACTION (ADR)	response to a harmful and unintended drug that occurs at therapeutic doses. We speak of serious ADR if: - endangers the patient's life - requires or extends hospitalization - determines persistent or permanent disability - causes death

Table 1: definition in pharmacovigilance[9]

The causal relationship between the adverse event of the patient and the intake of the therapy is defined on the basis of clinical, pharmacological, and also temporal criteria (in particular by evaluating, if possible, not only the dechallenge, or if the suspension of the treatment improves or heals the symptoms, but also the rechallenge, i.e., the re-exposure to increasing doses of the drug to evaluate the dose-response relationship). Most ADRs are dose-dependent and predictable, and above all, not serious, and only about 20% are serious and unpredictable, mainly related to individual immunological (IgE or T lymphocytes mediated) or idiosyncratic mechanisms. In this article, we will focus on severe ADRs and, in particular, on skin manifestations.[10][11]

Materials and Methods

An in-depth search was carried out starting from textbooks of pharmacology and pharmacovigilance, both on paper and from the online platform "Google Books," supplemented by the subsequent addition of articles such as reviews and original articles working on databases such as Scopus, ResearchGate, PubMed, and Google Scholar, typing in keywords such as "skin ADR," "severe drug reactions," "Lyell or Stevens-Johnson syndrome"; associated with specific compound names. They have also been integrated with the authors' knowledge in the toxicological and pharmacological fields.

Discussion

The skin is the most frequent target organ of ADRs, which represent 18-20% of the reports in the WHO database. Rashes and urticaria are the most frequent clinical patterns, usually of moderate severity, while rare (on the order of a few cases per million population) are ADRs associated with significant mortality and morbidity rates such as Stevens-Johnson syndrome, Lyell's syndrome, TEN (toxic epidermal necrolysis), and DRESS (drug rash with eosinophilia and systemic symptoms).[12] The clinical manifestations of cutaneous ADRs can derive both from the contact between the skin of a sensitized subject and the topical medicament (these are cases of allergic contact dermatitis or irritant contact dermatitis, with local reactions at the site of application and usually not serious) or from the development of more severe systemic hypersensitivity phenomena.[13] In these cases, it is possible that the drug behaves as an allergen or hapten, according to the classical mechanisms of Gell and Coombs, or that it generates direct non-immunological activation of the complement, as well as possible idiosyncratic phenomena, from metabolic alterations, from interactions, etc.[14] The drugs most causing these phenomena are NSAIDs, antibiotics (especially beta-lactams), sulfonamides (e.g., cotrimoxazole), anticonvulsants such as carbamazepine or lamotrigine, allopurinol, and contrast agents, as well as anticancer and biological drugs.[15] In relation to the clinical pictures, the most frequent are certainly erythema, of various types and extent, accompanied or not by subjective symptoms such as itching or burning.

Depending on the type, they can be divided into morbilliform, roseoliform, scarlatiniform, or pustular. They can also appear after 15-20 days from the suspension of the drug in question or within 24-48 hours from taking it. They are generally not associated with systemic symptoms and resolve without sequelae. Urticarial eruptions are also frequent, with itchy IgE-mediated wheals or mast cell release of preformed mediators (anaphylactoids, as in the case of opioids or muscle relaxants).[16][17]

The three images show three different severe cases of acute diffuse drug rashes

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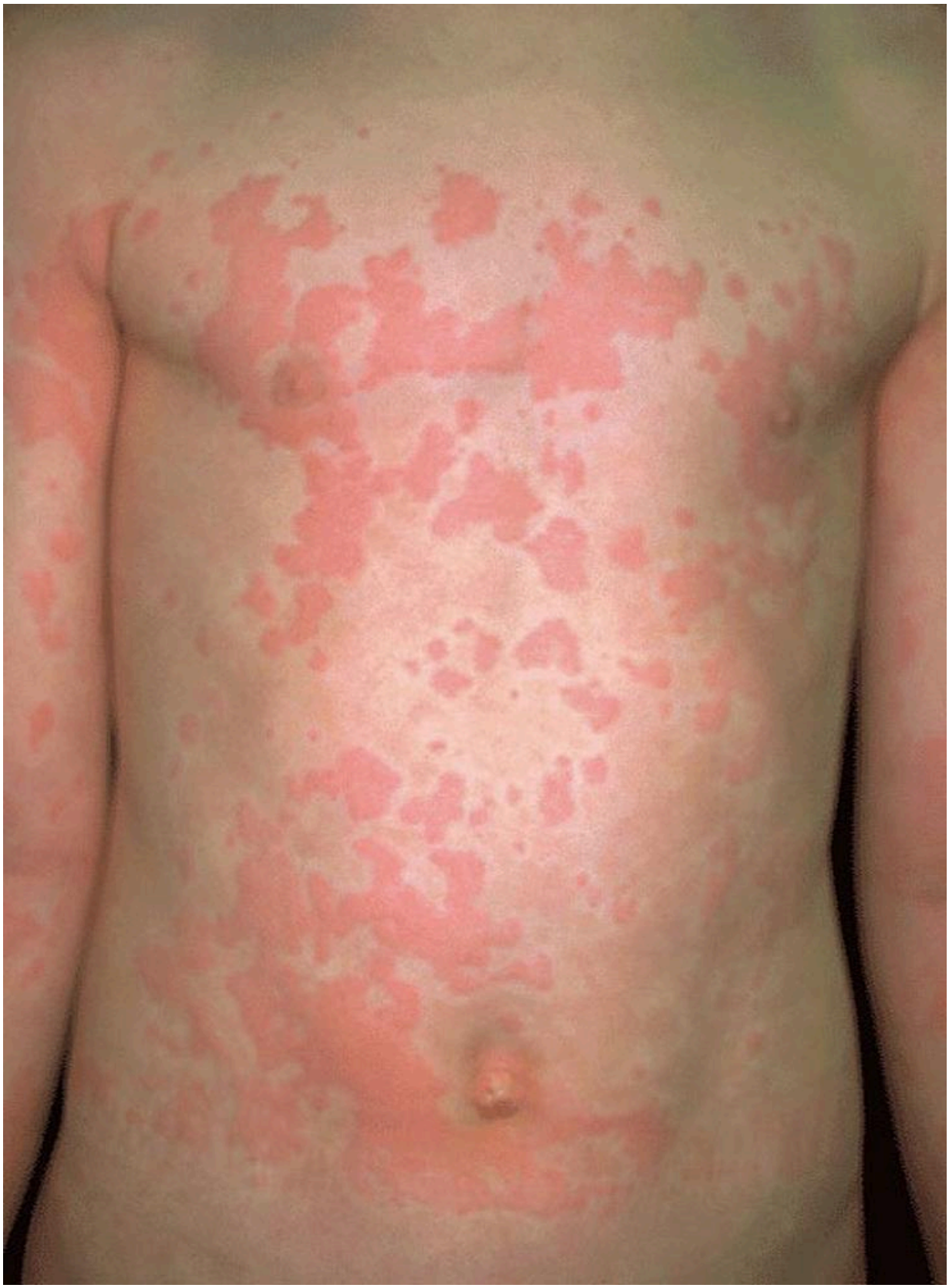

Image 1

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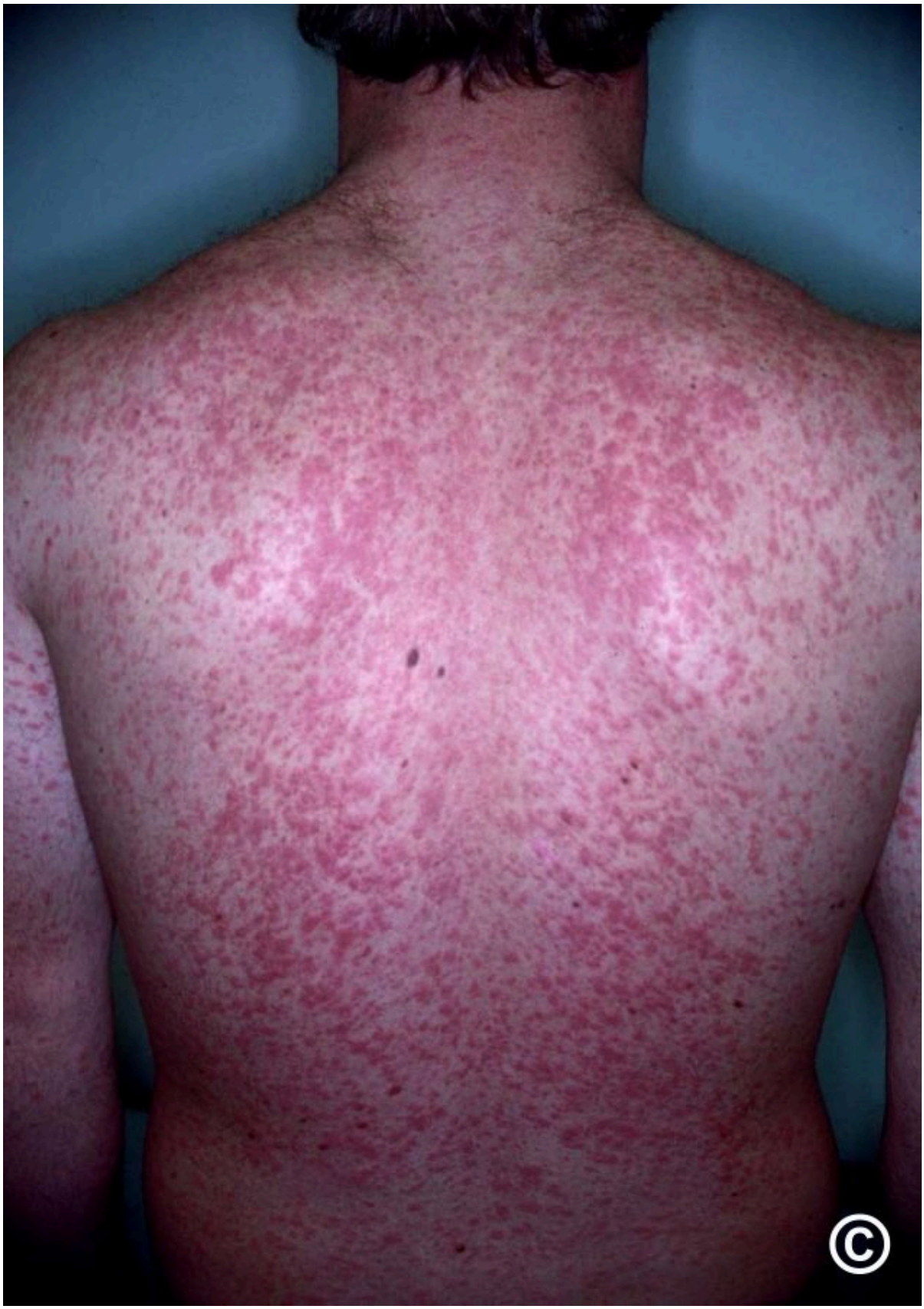

Image 2

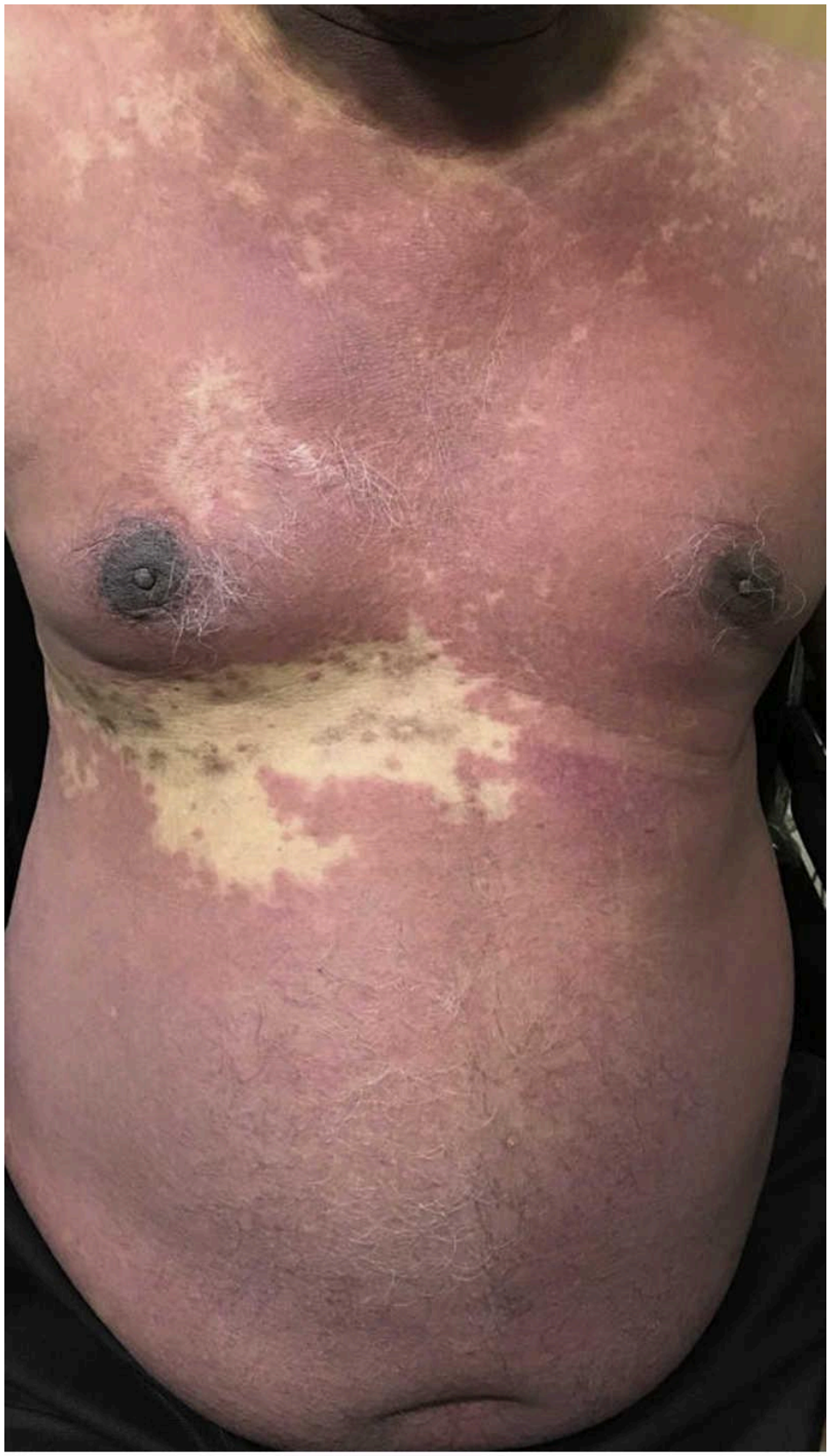

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Image 3

There are also less common forms of drug eruptions, such as lupus-like or psoriasiform ones, for example, following the intake of lithium salts, interferon, or beta blockers. In some cases, it is actually an aggravation or a patenting of the underlying disease.[18] Diagnosis is generally not difficult given the acute onset and recent history of taking the causative drug therapy. However, the well-known case of skin exanthema arising after taking a beta-lactam (usually amoxicillin or ampicillin) in patients with acute EBV infection (mononucleosis) or CMV (cytomegalovirus), two herpes viruses, deserves mention.[19][20] In some subjects, they can trigger an apparent drug rash following the administration of the aforementioned compounds even in the absence of a true allergy. Various hypotheses have been made; probably they are idiosyncratic reactions or, in any case, from non-allergic phenomena given the absence of specific IgE or new rashes at the subsequent rechallenge with the drug after at least 6 months. [21] Some very severe clinical pictures of cutaneous ADRs will now be described, rare but potentially fatal if not managed adequately.[22]

- ***erythroderma:*** is defined as a rare inflammatory skin disease with erythema and generalized exfoliative dermatitis that covers more than 80% of the body surface area and represents the maximum severity of various skin disorders[23]. In reality, the causes of such a clinical picture may be various; we will focus on the iatrogenic ones. Literature data show an index of 1-2 cases per 100,000 patients per year. The fundamental lesions are erythema, which involves all or almost all of the body surface, and scales of varying size, from fine or furfuraceous to lamellar. 14Other lesions may be present, such as edema, skin thickening, discoloration, or blistering. [24] Erythroderma involves a worsening of the patient's general condition and, apart from any itching or pain, there may be a compromised water and electrolyte balance, reduced oncotic pressure with edema, and altered mechanisms of body homeostasis. ADRs represent about 25% of erythroderma cases. Diagnosis of erythroderma is based on history and physical examination
- ***Rashes:*** Drug rashes, along with urticaria-angioedema, are the most common manifestations of cutaneous-mucosal ADRs. Rashes are extensive skin eruptions consisting of repetitive lesions; based on the type of lesions, they can be classified into maculo-papulosis, vesicular, or hemorrhagic.[25] In general, in drug rashes, compared to infectious ones, the lesions are more numerous and of a more intense color, they appear in patches, sometimes contain urticarial elements, and therefore are associated with itching. In the pathogenesis, we find as possible elements: a direct damage to the capillary wall (with consequent vasodilation, for example, due to the local deposition of immune complexes) or a damage to skin cells, by direct or indirect action of the antigen at the epidermal or dermal level, the lute being an important local immune system and vascular drainage.[26] The drugs most implicated in their pathogenesis are antibiotics, anticonvulsants, allopurinol, NSAIDs, but they have also been described for captopril, benzodiazepines, lithium, oral hypoglycemic agents, clonidine, and phenothiazines. Viral infections such as HIV, CMV, or EBV are important co-factors in the induction of these reactions. They often appear within 2 weeks of dosing as light reddish or salmon red, point to multi-sized, confluent patches. They usually affect the trunk, neck, and upper extremities. Sometimes they can manifest as purpuric lesions in the sloping areas of the limbs. They tend to disappear 1-2 weeks after stopping the drug.
- ***stevens-johnson and lyell syndrome:*** they are clinically similar, except for their distribution. According to a commonly accepted definition, the changes affect <10% of the body surface in Stevens-Johnson syndrome and> 30% of the body surface in toxic epidermal necrolysis; the involvement between 10 and 30% of the body surface is considered an overlap between Stevens-Johnson syndrome and toxic epidermal necrolysis. The prevalence of these disorders is 1-5 people / million. The incidence and / or severity of both conditions are higher in bone marrow transplant recipients, Pneumocystis jirovecii-infected HIV-positive patients, patients with systemic lupus erythematosus, and patients with other chronic rheumatic diseases. Drugs trigger more than 50% of Stevens-Johnson syndrome cases and up to 95% of toxic epidermal necrolysis cases[27]. The exact pathophysiological mechanism remains unknown: however, altered drug metabolism (e.g., inability to clear reactive metabolites) in some patients triggers a T-cell-

mediated cytotoxic reaction to drug antigens, according to one hypothesis, present in keratinocytes. CD8 + T lymphocytes have been identified as important mediators of blister formation. The results suggest that granulysin released by cytotoxic T cells and natural killer cells may play a role in keratinocyte death; the concentration of granulysin in the blister fluid correlates with the severity of the disease. Interleukin-15 has been shown to be increased in patients with Stevens-Johnson syndrome and toxic epidermal necrolysis and has been shown to increase granulysin production. Another theory involves interactions between Fas (a membrane receptor that induces apoptosis) and its ligand, specifically a soluble form of the Fas ligand released by mononuclear cells, which leads to cell death and blistering. A genetic predisposition has also been suggested[28][29]. Within 1-3 weeks of initiating therapy with the responsible drug, patients experience general malaise, fever, headache, cough, and keratoconjunctivitis. The macules, which often take on a target-like appearance, then appear suddenly, usually on the face, neck, and upper torso. In severe cases of toxic epidermal necrolysis syndrome, large layers of epithelium flake off throughout the body at pressure points (Nikolsky's sign), exposing exuding, painful, and erythematous skin. Painful scabs and oral erosions, keratoconjunctivitis, and genital disorders (e.g., urethritis, phimosis, and vaginal synechiae) are present in up to 90% of cases[13]. The bronchial epithelium can also flake off, causing cough, dyspnea, pneumonia, pulmonary edema, and hypoxemia.

Image 4 and 5: a case of Stevens-Johnson syndrome

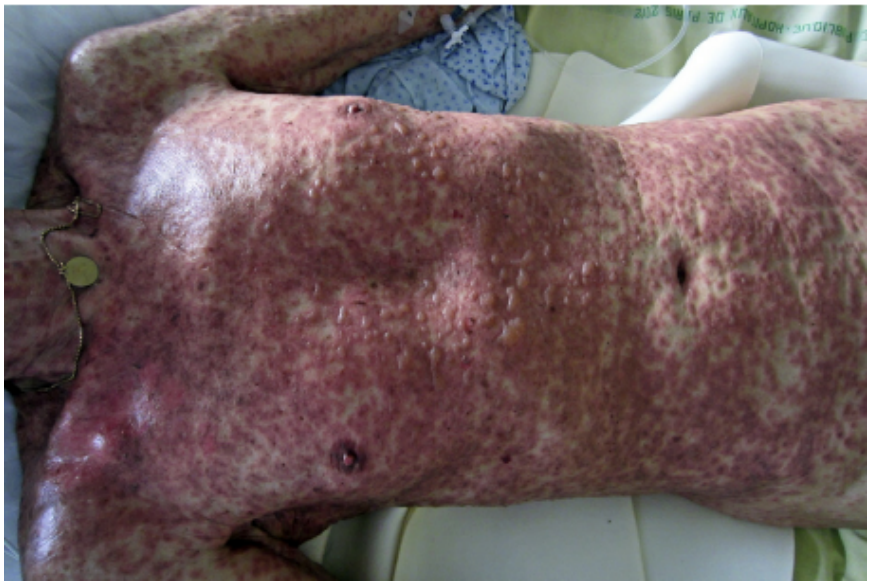

Image 4

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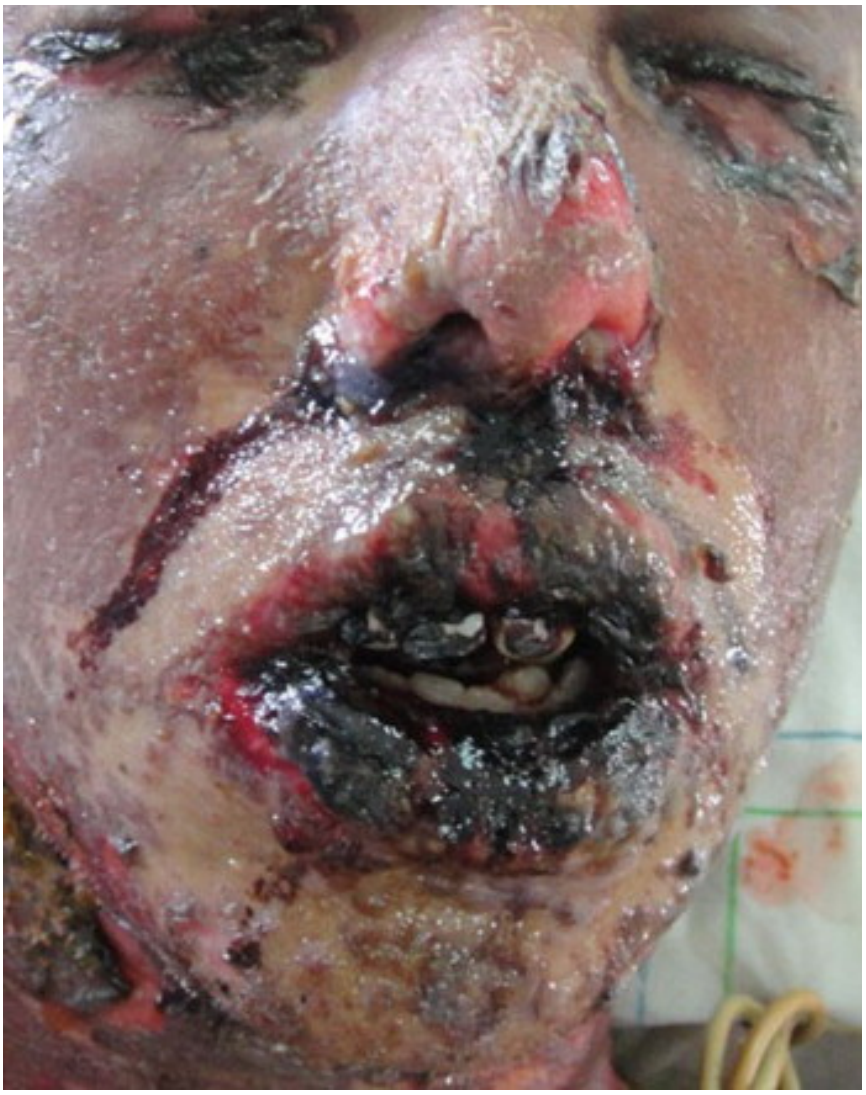

Image 5

Severe toxic epidermal necrolysis is similar to extensive burns; patients are acutely affected, may not be able to feed or open their eyes, and lose significant amounts of fluids and electrolytes. They are at high risk of infection, multiple organ failure, and death. With early therapy, the survival rate approaches 90%. The score for assessing the severity of toxic epidermal necrolysis (Severity-of-Illness Score for Toxic Epidermal Necrolysis (SCORTEN)) examines 7 factors within the first 24 hours of admission to the hospital of independent risk, to determine the mortality rate for a given patient[30].

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SCORTEN: mortality risk assessment scale for SJ and NET

- age over 40
- skin detachment greater than 10%
- heart rate over 120
- plasma bicarbonates less than 20 nmol / l
- blood sugar over 14 nmol / l
- urea over 10 nmol / l

- ***Drug Rash with Eosinophilia and Systemic Symptoms (DRESS):*** It's a severe form of cutaneous ADR whose presentation includes systemic symptoms (fever, general malaise, pharyngitis, and facial edema), polyadenopathy, rash (of which various types of lesions have been described, including urticarial, maculo-papular, and sometimes purpuric, in over 50% of the body surface), and above all eosinophilia, often severe, with at least one deep visceral affection (hepatitis, nephropathy, interstitial lung disease), but myocarditis, myositis, and central neurological manifestations have also been described[15]. During DRESS, viral reactivation is frequently observed, especially of EBV, CMV, and HHV6 and 7. The histological examination of the skin shows lichenoid lymphocytic infiltrates predominantly of TCD8 + mononuclear mononuclear cells, or epidermotrope with cellular atypia that can evoke the diagnosis of pseudo-lymphoma[31]. Evolution can be fatal in 5-10% of cases and, even when benign, it can take months or up to a year for complete resolution[32]. In the literature, the drugs most frequently associated with this syndrome include antiepileptics (e.g., carbamazepine, lamotrigine, and phenytoin) and allopurinol, as well as sulfonamides, minocycline, and vancomycin. More recently, in May 2016, the Food and Drug Administration issued a warning highlighting that olanzapine could cause DRESS syndrome. CARM (New Zealand Center for Adverse Reaction Monitoring) received 39 reports of DRESS syndrome between January 1, 2012, and December 31, 2016. The most frequently reported suspected drugs included allopurinol (13 cases), vancomycin (4 cases), piperacillin / tazobactam (3 cases), and sulfasalazine (3 cases).

In addition to the reactions described, it should also be remembered that several minor dermatological lesions have been described as associated with a wide range of pharmacological therapies, both as a new onset and as a worsening of a pre-existing dermatosis. For example, acne lesions caused by anti-EGFR drugs or by steroids, and psoriatic or lupus-like lesions related to hydralazine or sulfonamides, are known in the literature. The contribution of genetics has recently made it possible to clarify, for some cases, how there may be an individual predisposing susceptibility. For example, it has been shown that the presence of the HLA B1502 variant is associated, especially in people of Asian origin, with a severe skin hypersensitivity reaction to carbamazepine in 100% of cases, or how the HLA B5701 variant is instead associated with hypersensitivity to abacavir, and that this marker is indispensable in the development of this ADR such that it is necessary to carry out the genetic test before starting the therapy.

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FOCUS ON: CUTANEOUS ADRS FROM MONOCLONAL ANTIBODIES

Among the adverse effects from monoclonal antibodies (mAb), the cutaneous ones are among the most frequent in terms of incidence, although fortunately, in most cases, they are not serious or are in any case reversible effects. Various types of post-infusion skin reactions have been described, both acute (in terms of post-infusion rash) and after repeated or chronic exposure (and almost all types of elementary lesions have been associated with such ADRs, from urticarial to lichenoid or lupus-like psoriatic ones), but the most common occur following the use of antitumor mAbs and in particular those used in immunotherapy[33]. By now, mAbs make up about 20% of drugs on the market and over 50% of those in pre-clinical development, so it is not surprising that, given their wide use, these effects are also very frequent. For example, in the case of immune checkpoint inhibitory mAbs (anti-PDL1, anti-PD1, or anti-CTLA4), they are observed in more than one-third of the treated patients, mainly in the form of a maculopapular rash (eczema-like spongiotic dermatitis) and pruritus. A wide range of other dermatologic manifestations can also occur, including lichenoid reactions, psoriasis, acneiform rashes, vitiligo-like lesions, autoimmune skin diseases (e.g., bullous pemphigoid, dermatomyositis, alopecia areata), sarcoidosis, or nail and oral mucosal changes. In addition, the use of anti-CTLA-4 and anti-PD-1 therapies in combination is associated with the development of more frequent, more severe, and earlier cutaneous irAEs compared to single agents[34]. In most cases, these dysimmune dermatologic adverse events remain self-limiting and readily manageable.

Conclusions

Severe skin ADRs are generally rare or very rare reactions, but they can lead to high mortality rates if not diagnosed and managed quickly and in the best possible way. It is important to keep in mind that, although rare, there are patients at greater risk of developing them, such as those with a history of allergies, familiarity, and, above all, those exposed to particular categories of drugs such as antiepileptics or some antibiotics. It is also important for all healthcare professionals to adequately and promptly report these ADRs by filling in the paper forms from the AIFA website or through the free access portal "vigifarmaco" to keep the data updated on the real incidence of such cases.

Conflict of Interest Statement: The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

A.M. and E.M. DECLARE: not to find themselves in situations of incompatibility or in conditions of conflict of interest, also potential.

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Author Contributions: All authors read and approved the final version of the manuscript. We worked in an integrated way on the development of the article, contributing both to the drafting of all the paragraphs and to the complete bibliography and research on the site: E.M. came up with the idea of writing the article. E.M. initiated the work and helped to implement the search for sources and developed the theory, and A.M. evaluated the sources used and implemented the pathophysiological aspects. Together, A.M. and E.M. verified the methods, investigating the specific aspect, and A.M. oversaw the results of this work. All authors discussed the results and contributed to the final manuscript.

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