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DRUG ERUPTION

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Abstract

Drug eruption is effect of a drug that occurs at doses used for prevention, diagnosis, or treatment. Drugs that are either prescribed by a doctor, or without a doctor's prescription. Currently there is a drug eruption in developed countries around 1-3%, while in developing countries around 2-5%. Eruption of drugs for skin diseases or other systemic diseases in the form of drugs, exanthematous eruption, urticaria eruption, pustular eruption, Fixed Drug Eruption (FDE), SSJ/TEN, and lichenoid eruption. Exanthematous eruption is the most common form of drug eruption. In establishing the diagnosis of drug eruption, a final examination must be used and a careful prior evaluation. Management of drug eruption takes precedence over the cessation of the causative drug, additional therapy is needed related to the severity of the reaction. Proper diagnosis and management is needed to increase the patient's life expectancy. Prevention of eruption recurrence is done by providing education about drugs that cause drug eruptions for patients and asking patients to replace the use of these drugs. Therefore, the correct diagnosis of the type of skin reaction is important, as it helps to better define the likely latency and subsequently the culprit drug.

Introduction

Drug eruption is an abnormal response to a drug ingredient or its metabolites that occurs in a person after taking the drug in a susceptible normal dose. Drug eruption can arise after the use of drugs, both drugs from a doctor's prescription, or without a doctor's prescription, herbal medicines and other natural medicines. Drugs taken for three months, especially during the initial six weeks, can be suspected as a major cause of drug eruption (exceptions to drug-induced lupus, pemphigus induced drugs and cutaneous pseudolymfoma induced drugs because they are frequently caused drugs).[1]

Handling of drug eruptions often experiences delays because of symptoms that are not specific, similar to other diseases, and the time of occurrence also varies. Lack of education and knowledge of patients about the drugs that cause eruptions also cause repeated eruptions. Severe drug eruption can cause death, so it is necessary to prevent the recurrence of drug eruption.[2]

Result and Discussion

I. Definition

Drug eruptions are defined by the World Health Organization as any noxious, unintended, and undesired effect of a drug that occurs at doses used for prevention, diagnosis, or treatment. However, most cutaneous reactions to drugs are indeed drug induced allergic reactions. Drug induced allergic reactions can present with a myriad of cutaneous manifestations. Cutaneous drug eruptions can range from an asymptomatic rash to a life threatening emergency. Because of the high frequency, morbidity, and potential mortality associated with drug eruptions, it is important to be able to promptly recognize, workup, and treat patients with possible drug reactions.[3,4]

II. Epidemiology

A study conducted by Nandha R. and colleagues in 2011 showed that eruptions in developed countries were around 1-3%, whereas in developing countries around 2-5%. This is similar to the study conducted by Chatterjee S and colleagues in India in 2006 that eruption occurred in 2.66% of patients.[2]

III. Pathophysiology

The precise mechanism of adverse drug eruption is unknown but most are likely the result of immune mediated reactions. Different immune responses cause distinct cutaneous reaction patterns. Type I hypersensitivity is defined by the cross-linking of IgE receptors that results in mast and basophil degranulation, releasing chemical mediators, such as histamine and leukotrienes. This type of hypersensitivity manifests as urticaria, angioedema, anaphylaxis. Type III hypersensitivity involves antigen-antibody complexes that formand deposit in the skin and small vessels. Examples include serum sickness and vasculitic drug eruptions. Type IV or delayed type hypersensitivity is defined by sensitized T cells that are reintroduced to an antigen, resulting in a release of cytokines, which then activate monocyte and macrophages. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are manifestations of type IV hypersensitivity reactions. Despite the differences in rates of drug eruptions, virtually all studies have found morbilliform and urticarial reactions the most common types of drug eruptions accounting for approximately 94% of drug eruptions. Antibiotics are notorious offenders. Over-all, the most common offending drugs that cause cutaneous drug eruptions include amoxicillin,

trimethoprim-sulfamethoxazole, ampicillin, semisynthetic penicillins, blood, and blood products.[4]

IV. Classification

1. Exanthematous Drug Eruption

Exanthematous drug eruptions (also called morbilliform or maculopapular drug eruptions) are the most common drug-induced eruptions. That is characterized by erythematous macules evolving in papules from 1 to 5 mm in diameter and may coalesce in plaques. Exanthematous drug eruption involves face, neck, or upper trunk and tipically spreads bilaterally and symmetrically toward the limbs. Exanthematous drug eruption could be accompanied by pruritus and mild fever (temperature of <38.5°C). Exanthematous drug eruption is self-limiting and resolves within 7-14 days after stopping the drug. At the first drug exposure, lesions appear after a sensitization phase, 5-14 days after the start of therapy and sometimes after drug discontinuation. In previously sensitized patients, skin lesions develop following re-exposure to the same drug in 6 hours to 5-7 days. The most common implicated drugs include beta-lactams, sulfonamides, and antiepileptic medications.[4,6]

Exanthematous drug eruption occours due to delayed (type IV) hypersensitivity reactions. Classically, antigen-presenting cells present haptens, composed of the drug or its metabolite bound to a protein or peptide, to naive T cells. These antigen-specific T cells proliferate, infiltrate the skin, and release cytokines, chemokines, and other proinflammatory mediators that are responsible for the signs and symptoms of the drug-related rash. According to an alternative theory known as the p-i (pharmacologic interaction of drugs with immune receptors) concept, small-molecule drugs or their metabolites, which are not complete antigens, activate T cells directly by binding to T-cell receptors. Irrespective of the mechanism that elicits a T-cell response to a drug, it is not known why only a minority of patients receiving a given drug have a clinical reaction to it, whereas others have immunologic reactivity without a rash.[5]

The management is supportive. Pruritus can be treated with topical steroids, emollients, oral antihistamines. Second generation H1 blockers are associated with fewer sedative effects when compared with first generation H1 blockers. A post-inflammatory

hypopigmentation or hyperpigmentation may follow which vanishes over months or years, and sun avoidance or protection should be advised.[6]

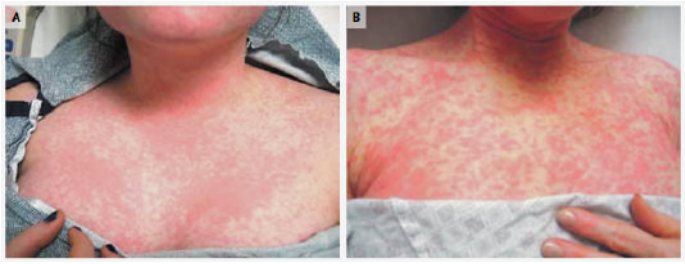

Figure 1. Exanthematous drug eruption

2. Drug-induced Hipersensitivity Syndrome (DIHS) atau Drug Reaction with Eosinofilia and Systemic Symptoms (DRESS)

Drug induced hypersensitivity syndrome (DIHS) or drug reaction with eosinophilia and systemic symptoms (DRESS), is a multiorgan systemic reaction characterized by rashes, fever, lymphadenopathy, leukocytosis with eosinophilia and atypical lymphocytes, and liver dysfunction. The disease usually starts abruptly with maculopapular mor-billiform exanthema with fever of >38C, 2-3 weeks after the introduction of the drug. Sometimes, there may be anupper-airway infection like prodrome, suggesting viral infections. The cutaneous lesions usually begin as patchy erythematous macules, pustular, target like or eczema like lesions, which may be slightly purpuric and can become confluent. The lesions are symmetrically distributed on the trunk, face and extremities. The skin manifestations of DIHS are maculopapularrash, erythema multiforme, exfoliative dermatitis, acute gen-eralized exanthematous pustular dermatosis-like eruption,and erythroderma. DIHS/DRESS is associated with the reactivation of herpes viruses, especially human herpesvirus 6 (HHV-6) and cytomegalovirus (CMV), in patients on long-term drug therapy. DIHS/DRESS is usually associated with drugs, including carbamazepine, phenytoin, phenobarbital, lamotrigine, dapsone, mexiletine, salazosulfapyridine,allopurinol, and minocycline.[7,8]

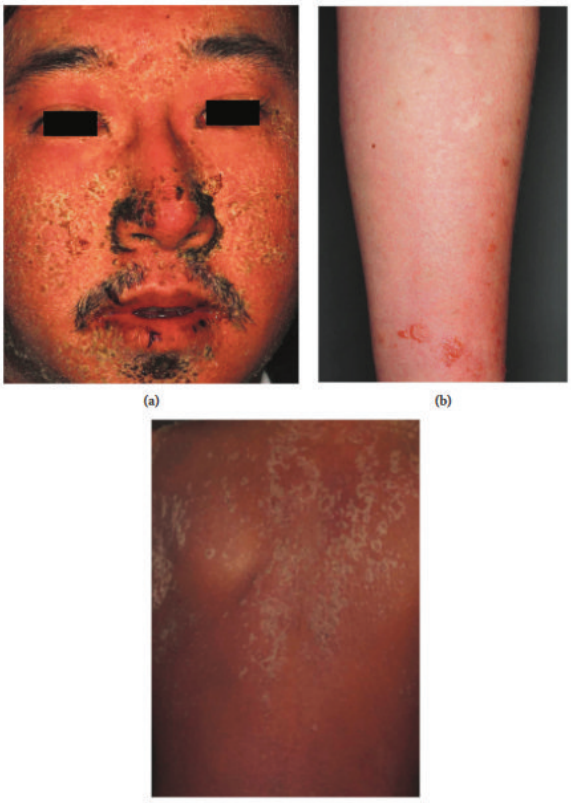

Figure 2. DIHS / DRESS

3. Urticaria

Urticaria is characterized by recurrent, pruritic, wheals with pale of the dermis and/or angioedema due swelling of lower dermis and subcutis or mucous membranes, central swelling and surrounding epidermal erythema which can appear over any part of the body. The lesions can range in size from a few millimeters to several centimeters in diameter and are often transient, resolving within about 24 hour without scarring; however, some lesions may last up to 48 hour. Drug induced urticaria is due to mediators, including histamine, and citokines released by activated mast-cells. Mast-cells can be degranulated by an IgE-mediated mechanism or directly by the drug. Mast cell degranulation leads to the rapid release of various inflammatory mediators, such as histamine, leukotrienes and prostaglandins, which, in turn, cause vasodilation and leakage of plasma in and below the skin.[9,10]

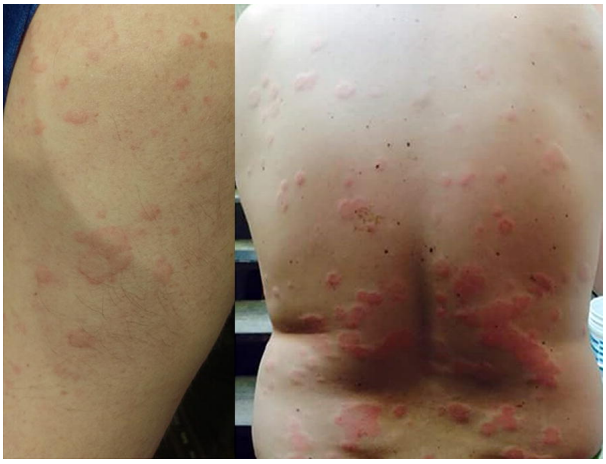

Figure 3. Urticaria

4. Acute Generalized Exanthematous Pustulosis

Acute generalized exanthematous pustulosis (AGEP) is drug reaction, characterized by an acute onset of mainly small non follicular pustules on an erythematous base and spontaneous resolution usually within two weeks. The acute phase of the disease is characterized by fever (>38 °C) and leukocytosis (neutrophilcounts above 7×109/l). Lymphadenopathy, a slightly reduced creatinine clearance, or a mild elevation of liver enzymes may be present, but visceral organ involvement is rare. AGEP usually resolves rapidly within 1–3 days after withdrawal of the causative agent leaving a characteristic collaret shaped desquamation pattern. Aminopenicillins, pristinamycin, sulphonamides, quinolones, hydroxychloroquine, terbinafin and diltiazem are the most frequent causative drugs.In particular cases, AGEP is induced by bacterial, viral or parasitic infections (e.g., parvovirus B19, mycoplasma, cytomegalovirus, coxsackie B4, Chlamydia pneumoniae, Escherichia coli, and echinococcus), spider bites, herbal medications, lacquer ,mercury and even psoralen combined with ultraviolet A (PUVA) treatment.[11,12]

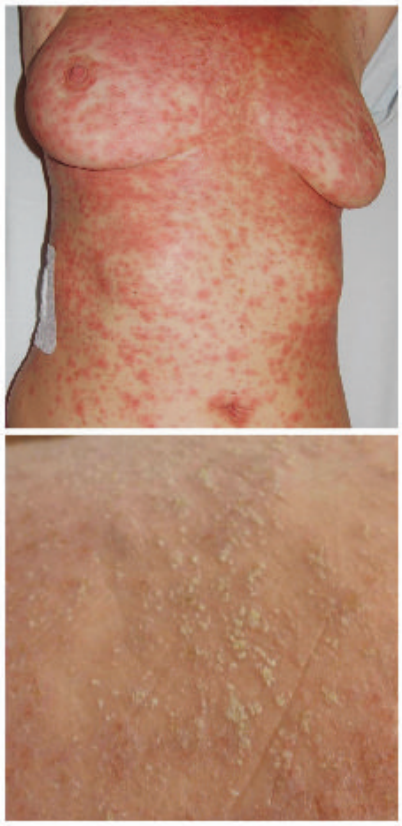

Figure 4. Acute Generalized Exanthematous Pustulosis

5. Stevens-Johnson syndrome and toxic epidermal necrolysis (SSJ&TEN)

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are acute life threatening mucocutaneous reactions characterized by extensive necrosis and detachment of epidermis. Clinically, SJS and TEN are characterized by erythematous macules, papules, plaques, vesicles and bullae. Target lesion with bull's eye appearance is characteristic of SJS and TEN. Non-specific symptoms such as fever, stinging eyes, and discomfort upon swallowing precede the cutaneous onset of TEN and SJS by hours to days. The vagina and penis can blister , and damaged skin in these sites may be over looked if not pointed ou tto doctors. As the skin heals,it may look darker or lighter than before. Hair and nails may fall out and regrow differently. The vagina and penis can be permanently scarred. The eyes may remain dry, and some vision may be lost. The mouth may be scarred and dry, leading to tooth decay. More than 100 drugs have been associated with SJS and TEN, most commonly implicated are anti-epileptics, sulphonamides, beta lactam antibiotics, non-steroidal antiinflammatory drugs, carbamazepin and allopurinol. They are

severe forms of hypersensitivity reaction mediated by cytotoxic T lymphocytes to a number of noxious stimuli predominantly drugs via perforin-granzyme route, FAS(CD95)-FAS ligand pathway or nitric oxide synthase route in susceptible individuals.[13,14]

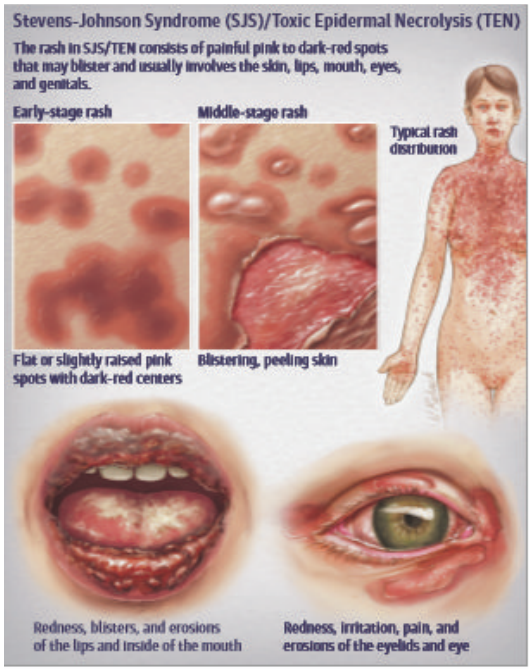

Figure 5. SSJ/TEN

6. Fixed Drug Eruption

Fixed drug eruption is a focal, circumscribed patch or plaque or a more extensive mucocutaneous reaction pattern occurring at same site each time the same drug is ingested. FDE is a delayed type IV hypersensitivity reaction. The drugs causing fixed drug eruptions are antibiotics (trimethoprim, amoxicillin), nonsteroidal anti-inflammatory drugs (mefenamic acid, naproxen) and systemic antifungal agents (fluconazole), paracetamol, sulphasalazine, anti infective medications (fluconazole, tetracyclinesand trimethoprim) cotrimoxazole, tetracycline, and ampicillin. Most fixed drug eruptions are asymptomatic, but swelling, pruritus or pain may be reported. Restlessness, dysuria and urinary retention have been reported in boys with genital fixed drug eruption. FDE is first evident as a red or violaceous circular plaque with a dusky-grey center. The eruption may be solitary, a localized cluster, or diffuse. FDE can appear at any skin site but targets areas with thin skin, such as the lip mucosa, genitals, and perianal sites. FDE occur up to 1 week after the

first drug exposure, and for subsequent exposures, between 30 min and 8 h afterwards. FDE is usually asymptomatic, but may be painful or pruritic.[15,16]

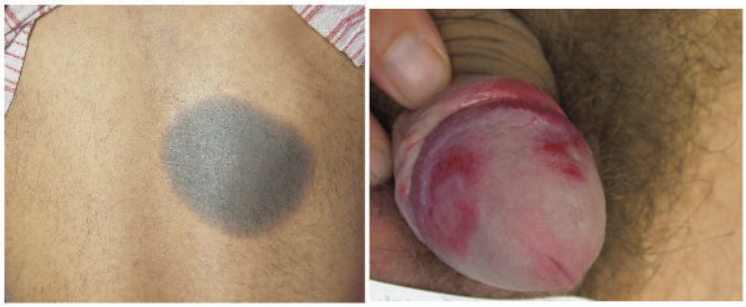

Figure 6. Fixed Drug Eruption

7. Lichenoid Drug Eruption

Lichenoid drug eruption (LDE), also known as drug-induced lichen planus. LDE has the clinical features of lichen planus, such as widely distributed symmetric skin rashes with or without Wickham striae, typical oral lesions, and similar histopathological findings (including epidermal parakeratosis and lympho-cyte infiltration into deeper layers of the dermis), but only LDE shows an elevated eosinophil number. Lycenoid eruption is caused by hydrochlorothiazides, furosemides, NSAIDs, aspirin, antihypertensives (ACE inhibitors, β-blockers, and calcium channel blockers), terazosin, quinidine, pravastatin, phenothiazine, anticonvulsants, anti-tuberculosis drugs, β-blockers, and calcium channel blockers), terazosin, quinidine, pravastatin, phenothiazine, anticonvulsants, anti-tuberculosis drugs, ketoconazole, including gold.[17,18]

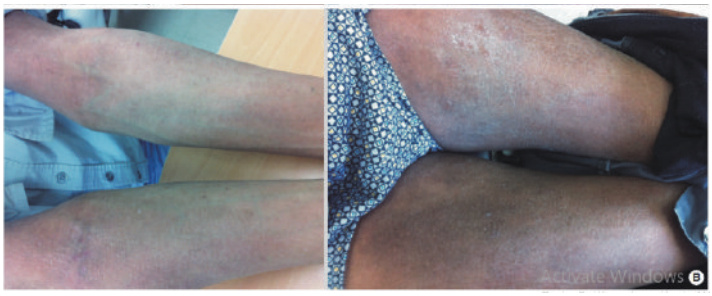

Figure 6. Lichenoid Drug Eruption

V. DIAGNOSIS

In history taken, things that need to be asked to the patient are as follows:[19]

1. History of drug use systemically (amount and type of drug, dosage, method of administration, duration of administration, sequence of effect of exposure to sun exposure) or contact of drug on exposed skin (erosion, excoriation, ulcer).
2. A history of the appearance of skin disorders with the time interval with the time interval of drug administration, whether arise immediately, a few moments or hours or days. Skin disorders: erythema, papules, squama, urticaria, vesicles / eruption, erosion, excoriation to ulcers and nodes.
3. Systemic complaints
4. Personal and family atopic history, allergies to other allergens, and previous drug allergies.

VI. Management of Drug Eruption

In the eruption of the skin that opposes the soul, use of drugs that replace must be eliminated, followed by the cessation of drugs that can be eliminated from the drug elimination in the body. Although the use of corticosteroids in cutaneous reactions that are quite serious is still somewhat controversial, clinical agreement to give prednisone at a dose of 1-2 mg / kg / day. Antihistamines, topical corticosteroids, or use can be used to treat the disease. The evaluation of therapy depends clearly on the severity of the reaction. In mild eruptions, symptomatic therapy with emollients, topical corticosteroids and systemic antihistamines. In severe reactions, such as NET, management must be done in an intensive care unit. Support for correction, high-calorie nutrition and prevention of sepsis.[20]

Conclusion

Diagnosis could be difficult because drug eruption can like other diseases (e.g., viral infections). Rapid identification and withdrawal of the causative drug are critical, although it isoften difficult to determine the culprit drug in patients with polymedication. Therefore, the correct diagnosis of the type of skin reaction is important, as it helps to better define the likely latency and subsequently the culprit drug. On the other hand, an incorrect diagnosis can limit therapeutic options and increase the risk of using more toxic, less effective and more expensive drugs. A detailed history is necessary in order to evaluate the real occurrence of the adverse reaction.

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