Polypharmacy as a Risk Factor for Exanthematous Drug Eruption

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ABSTRACT
Cutaneous adverse drug reactions (CADR) are an unfavorable condition caused by drugs manifesting on the skin. Exanthemata's drug eruption is the most common manifestation. The symptoms are itchy rash and burning sensation at the lesion and can occur along with fever and pain. The most common types of drugs inducing CADR are antibiotics, non-steroidal, anti-inflammatory drugs (NSAID), and anticonvulsants. A 48-year-old woman with complaints of itching on the chest followed by both arms and legs. Complaints arose 8 days after surgical excision of the craniometrical tumors when the patient was treated with polypharmacy medications. The description of the lesions is regional, multiple, well-defined maculopapular lesions with erythema, crusts, and excoriation. The working diagnosis is exanthemata's drug eruption with ceftriaxone, paracetamol, and phenytoin as the suspected causative drugs. No history of drug allergy was known before. Polypharmacy can cause difficulty in making clinical decisions for discontinuing the suspected drugs and cause patient's comorbidity left untreated. Therefore, it is important to identify the type of drugs and drug interaction causing cutaneous adverse drug reactions and minimize the use of polypharmacy therapy if possible.

Keywords: *Exanthemata's drug eruption, Polypharmacy, Ceftriaxone, Paracetamol, Phenytoin.*

1. INTRODUCTION

Cutaneous Adverse Drug Reactions (CADR) is a disorder that arises in the skin due to the use of the drug [1,2]. About 10-45% of adverse drug reactions manifest on the skin and about 2-3% of patients require hospitalization as a result [2,3]. Several reactions occur on the skin, both mild to severe, such as exanthemata's drug eruptions, urticaria, Steven-Johnson Syndrome (SJS), and Toxic Epidermal Necrolysis (TEN)[1-3]. Several risk factors that influence the severity and frequency of CADR are polypharmacy, old age, female, liver and kidney disease, malignancy, diabetes, Human Immunodeficiency Virus(HIV), and certain subtypes of Human Leukocyte Antigen(HLA) [4]. CADR diagnosis has only been clinical, and most CADRs resolve on their own with discontinuation of the precipitating drug [2]. Various drugs can cause CADR, including cephalosporins, phenytoin, diclofenac, carbamazepine, and fluoroquinolones[2,5]. There is the various definition used for polypharmacy, but the most often one is the use of five or more drugs [6]. Polypharmacy can cause interactions between drugs and make it difficult to identify drugs that cause CADR [4,7]. This makes information related to drugs that most often cause CADR can help in providing clinical decisions regarding drug discontinuation, especially in polypharmacy therapy. The purpose of this case report is to provide information about drugs and the presence of polypharmacy risk factors that can cause exanthemata's drug eruptions.

2. CASE REPORT

A 48-year-old woman was consulted from the neurosurgery department to the dermatology and venereology department with complaints of itching and redness on the chest, hands, and feet on the 10th day after surgical excision of a craniocervical meningioma. Symptoms of itching began to appear 8 days after the patient underwent surgery. At that time, the patient received various kinds of drugs, including ceftriaxone which was then replaced with cefixime after 9 days of surgery, fentanyl, paracetamol, phenytoin, tranexamic

acid, ondansetron, *Channa striata* extract, loperamide HCl, flunarizine, and rillus (contains probiotics and prebiotics). The patient has no fever, cough, and rhinorrhea. The patient had no history of food and drug allergies. The patient had a history of type 2 diabetes mellitus. On physical examination, there were multiple erythematous maculopapular lesions with crusting and excoriation on the chest, hands, and feet (Figure 1 and 2). The results of laboratory tests on the 3rd day after surgery showed leukocytosis, thrombocytopenia, and neutrophilia.

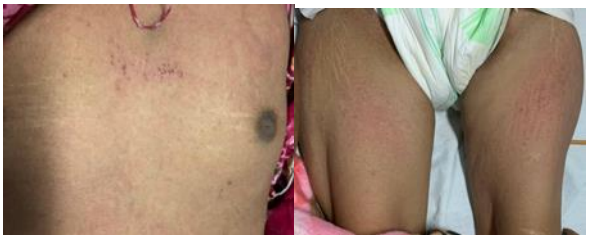

Figure 1. Chest and thighs with multiple erythematous maculopapular lesions with crusting and excoriation

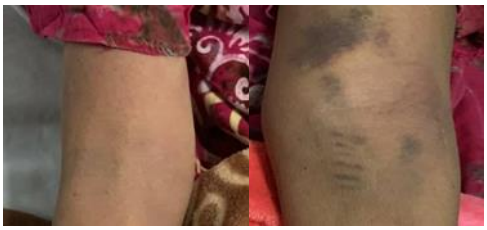

Figure 2. Cubital fossa of right and left hand

The working diagnosis in this patient was exanthematous drug eruption. Therapeutic advice from the dermatology and venereology department was the discontinuation of the suspected causative drugs and supportive therapy, namely methylprednisolone 2x16 mg, cetirizine 1x10 mg, desoxymethasone cream 0.25%, and chloramphenicol cream 2%. The day after being consulted, several drugs were discontinued, including cefixime, folic acid, phenytoin, paracetamol, and *Channa striata* extract. The patient's condition showed improvement (Figure 3).

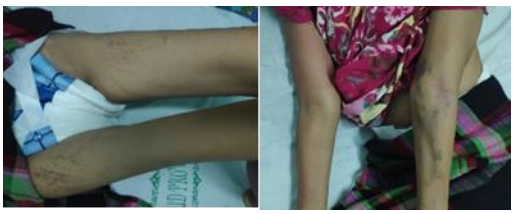

Figure 3. Improvement on patient's thighs and cubital fossa

3. DISCUSSION

In this case, the patient was diagnosed with an exanthematous drug eruption. The exanthematous drug eruption has the most common symptoms of itching and burning, can be accompanied by fever and pain. Complaints generally occur 4-14 days after exposure to the triggering drug. The differential diagnosis, in this case, is Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and viral exanthem. DRESS can be excluded because there is no fever and complaints are generally felt 14-42 days after drug exposure accompanied by lymphadenopathy and eosinophilia. Viral exanthema is generally preceded by prodromal symptoms such as fever, cough, and sore throat, but in this case, there was no history [2,4,8].

Administration of topical and systemic corticosteroids is intended to relieve inflammation caused by type IV hypersensitivity. Complaints of itching can be reduced by systemic antihistamines [1,9]. Topical antibiotics prevent secondary infection from open wounds caused by scratching[10]. The main therapy that needs to be done is the discontinuation of drugs suspected of causing drug eruptions so that identification of these drugs is important[9,11,12].

Cutaneous adverse drug reactions are usually caused by antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), and anticonvulsants[3,5,11]. The cause that is often found as a trigger for the exanthematous drug eruption is antibiotics[13,14,15]. Classes of antibiotics that often cause this condition are β-lactam such as penicillins, cephalosporins, and carbapenems[3,13,15]. According to Janardhan B et al, amoxicillin (39.77%), ampicillin (19.88%), and cephalosporins (22.22%) were found to be the originator of the drug on the exanthematous drug eruption[13]. Research conducted by Jha N et al showed similar results with cephalosporins at 22.73% and carbapenems at 17.27%[3]. Several cephalosporin drugs were found to trigger cutaneous adverse drug reactions, including ceftriaxone, cefixime, and cefotaxime[14,16,17].

Based on several studies, anticonvulsant often causes exanthematous drug eruptions are phenytoin, carbamazepine, and valproate[13,15,18]. According to research conducted by Janardhan B *et al* and Tegta G et al, phenytoin was found to be the cause of 13.45% and 2.47%, and carbamazepine was responsible for 4.68% and 2.06% of the incidence of exanthematous drug eruptions[13,18].

Non-steroidal anti-inflammatory drugs are the second most common trigger for cutaneous adverse drug reactions[3,19,20]. Diclofenac, paracetamol, and ibuprofen are NSAIDs that have been mentioned as the cause of exanthematous drug eruptions in several studies[5,19,20]. Research by Sharma S et al showed diclofenac (9.7%) as the most common trigger for the eruption of drugs belonging to the NSAID class[5]. In another study, paracetamol is responsible for 15% of all cases of exanthematous drug eruption[19]. The results obtained by Mahatme et al. showed that ibuprofen caused an exanthematous drug eruption of 16.6%[20]. Another

NSAID that was found to cause exanthematous drug eruption was nimesulide with a percentage of 0.82%[18].

Cutaneous adverse drug reactions have several risk factors and one of them is polypharmacy[4,7,21]. Based on research by Jatana G et al., exanthematous drug eruption can be caused by one drug (78.9%) or several drugs (21.1%)[22]. In the study conducted by Chopra D et al., 79.9% of patients had at least one predisposing factor and one of the most common was polypharmacy[15]. Similar findings were found in the study of Tegta G et al. with polypharmacy (33.65%) as a frequent risk factor [18]. Talib N et al. showed a 13% increase in the occurrence of cutaneous adverse drug reactions when using two drugs and 82% increase if the drugs used were $\geq$ 7, which was thought to be due to interactions between drugs[7]. Some studies have found some drugs used together can lead to CADR, such as β-lactam with β-lactamase inhibitor, sulfonamide with DHFR inhibitors, NSAIDs with NSAIDs, and fluoroquinolone with antiamoebic[21]. The existence of polypharmacy will make it difficult to determine the drug suspected of causing cutaneous adverse drug reactions. The causality assessment method cannot provide information regarding the suspected drug trigger in patients with polypharmacy, especially on concurrent drug administration. In the use of polypharmacy therapy, discontinuation of the suspected drug concurrently can cause the patient's comorbidities to be left untreated [4].

4. CONCLUSION

This case provides information regarding the identification of drugs suspected of causing exanthematous drug eruptions in patients on polypharmacy therapy. The existence of polypharmacy causes clinical decisions to discontinue drugs that are suspected to be longer and discontinuation of multiple drugs will cause comorbidities in patients to be untreated. This makes it important to know the types and drug interactions that often trigger cutaneous adverse drug reactions and reduce polypharmacy therapy if possible.

CONSENT FOR PUBLICATION THE IMAGE

The authors have confirmed during submission that patient consent has been signed and collected in accordance with the journal's patient consent policy.

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