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REACTIVATION OF MACULOPAPULAR DRUG ERUPTION LESIONS SUSPECTED TO BE CAUSED BY ALLOPURINOL DURING 72 HOURS-PATCH TEST: A CASE REPORT

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Abstract

Maculopapular drug eruption is a delayed-type T-cell-mediated hypersensitivity reaction to a drug that is most commonly encountered within one week of suspected drug exposure. Allopurinol is a drug that is often found as a cause of drug allergic eruptions. The drug patch test can be used to identify the causative agent of a drug eruption. A 56-year-old man came with the chief complaint of itchy red patches on his face, chest, back, hands and feet for the past two weeks. The patches appeared five days after the patient took allopurinol for his hyperuricemia. The patient was diagnosed with maculopapular drug eruption with suspected to be caused by allopurinol. Six weeks after the patient was free from any lesions and eligible, a patch test was performed but the results were negative in all chambers on all reading days. At 72 hours after the patch test, there was reactivation of the skin lesions which obscured the patch test results. Maculopapular drug eruptions can be triggered by drug metabolites or drug absorption from the patch test itself is sufficient to cause reactivation.

Keywords: *Teacher Emotional Labor, Teacher Work Engagement, Teacher Commitment, Teacher Performance.*

Introduction

Maculopapular drug eruption or often referred to as morbiliform drug eruption is a delayed-type hypersensitivity reaction to drugs characterized by itchy erythematous macules, patches, papules or plaques without vesicles, bullae, pustules or systemic organ involvement. Maculopapular drug eruptions occur within three weeks of suspected drug exposure and may occur 1 to 2 days after drug discontinuation. Resolution may occur spontaneously within 7 to 14 days, the erythematous lesion turning into hyperpigmented with scaling (N Engl J Med. 2012); (McGraw-Hill Education; 2019) reported the prevalence of maculopapular drug eruptions worldwide is 31-95% of all allergic drug eruptions and maculopapular drug eruptions occur in 1 in 3000 exposures to anticonvulsant

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agents, lamotrigine, sulfonamides, antibiotics, dapsone, nitrofurantoin, nevirapine, minocycline, metronidazole and allopurinol (Karger. 2007). Data on the prevalence of maculopapular drug eruptions caused by allopurinol in Indonesia have not been reported (J Kesehat Andalas, 2018).

A drug patch test can be performed to identify the causative agent of a drug eruption and is relatively safe and easy to perform (Mahajan VK et al, 2013). Indications for patch testing are people with contact dermatitis, other skin diseases that may be triggered by contact dermatitis (atopic dermatitis, psoriasis, dyshidrosis), chronic dermatitis with no known cause and people with occupational contact dermatitis. Patch testing can also be used to find the causative agent of allergic drug eruptions and is also called a drug patch test which can be performed using the suspected drug preparation (Bras Dermatol. 2012); (Barbaud A, 2005).

Reactivation of drug allergic eruption lesions after patch testing has not been widely reported. (Salman A et al, 2019) in Turkey reported reactivation of cases of acute generalized exanthematous pustulosis (AGEP) after a patch test with ceftriaxone, while Cordoba et al (2016) in Spain reported reactivation of a drug rash with eosinophilia and systemic symptoms (DRESS) lesion after a patch test. with trimethoprim-sulfamethoxazole (Córdoba S et al. 2016); (Shalom R. 208) Reactivation of DRESS lesions due to allopurinol has been reported by Shalom et al in 2008 in Israel, cases of recurrence of maculopapular drug eruption due to allopurinol after patch testing have not been reported (Stern RS. 2012).

In cases of reactivation of allergic drug eruptions after patch testing, case-specific management should be given immediately. This paper reports a case of reactivation of maculopapular drug eruption after patch testing with allopurinol. The purpose of writing this paper is to increase knowledge and increase awareness about reactivation of allergic drug eruptions after patch testing even though the patch test results are negative.

Research Methods

The preparation of drug paste test kits by using IQ Ultra Chamber (Chemotechnique, Sweden), hypoallergenic plaster and permanent markers, cotton swabs soaked in 70% alcohol and drug paste test materials. Patients were tested using the drugs of ticagrelor 10%, ramipril 5%, atorvastatin 10%, furosemid 10%, spironolakton 10%, bisoprolol 10%, acetylsalicylic acid 10%, alopurinol 10% and alopurinol 20% in petrolatum. The patch test was performed six weeks after the patient was free of lesion, corticosteroid-free and antihistamine-free, the patch test was performed on the upper back. Patients were asked not to wet the back area, reduce excessive activity so that the patch test does not shift, come off or get wet with sweat, do not scratch, sleep on your back or lean on your back and do not consume corticosteroids and antihistamines for 4 days. The patient was re-asked for control to be removed on 48 hours (day 2), 72 hours (day 3) and 96 hours (day 4) readings after the installation of the patch test.

At 48 hours after the installation of the patch test, the control patient and chamber were removed slowly. After waiting 20 minutes for the skin contours to return to normal, negative results were obtained in all chambers on all days of reading the results. At 72 hours after the installation of the patch test, a reactivation of skin lesions in the form of macula, patches and papules of erythema was partially hyperpigmented with multiple hyperpigmentation accompanied by a squama that began to close the installation area of the patch test so as to obscure the readings of the results. At 96 hours after the installation of the patch test, the skin lesions became more widespread and thickened to cover the patch test installation area so that the patch test results were judged invalid. Based on autoanamnesis, physical examination and paste test examination, our patients are diagnosed with the eruption of the maculopapular drug suspected to be caused by allopurinol.

Results and Discussion

Maculopapular drug eruption is a delayed type hypersensitivity reaction mediated by T cells to drugs that has a morbilli rash-like appearance. Maculopapular drug eruption is the most common type of drug eruption. Drugs that have a high risk (5-20%) for causing a maculopapular drug eruption are penicillins, carbamazepine and allopurinol, followed by a moderate risk (3-5%) which include sulfonamides, non-steroidal anti-inflammatory drugs, hydantoin derivatives, isoniazid, chloramphenicol, erythromycin, and streptomycin, followed by low risk (<1%) namely barbiturates, benzodiazepines, phenothiazines and tetracyclines (Wolff K et al, 2017); (Yunihastuti E, 2014) in this case, the patient had a history of taking allopurinol since five days before the onset of skin lesions.

The pathophysiology of maculopapular drug eruptions is mediated by type IV or delayed type hypersensitivity reactions. The pathogenesis is unclear but is an immune-mediated reaction, either through a hapten-dependent or hapten-independent pathway. A hapten is a small molecule that can trigger antibody production when it binds to a larger protein. According to the hapten dependent pathway, drugs will be metabolized in the liver by cytochrome P450 enzymes into reactive metabolites which then bind to proteins and are presented via human leukocyte antigen (HLA) to T cells. Meanwhile, in the independent hapten pathway, the drug itself without undergoing metabolism can activate T cells by binding to the major histocompatibility complex (MHC) or T-cell receptor (TCR). T cells will infiltrate the skin, produce cytokines (Barbaud A, 2013); (Aquino MR, 2013).

Clinical manifestations of maculopapular drug eruptions are erythematous macules and papules which over time confluent into multiple erythematous patches and sometimes become erythroderma accompanied by scaling, have a symmetrical distribution and in adults are almost always found on the trunk and extremities, whereas in children it is more common on the face and extremities (Wibisono Y, 2020); (Teo YX, 2007) In this case in the facial region, anterior trunk, posterior trunk, superior and inferior extremities bilaterally found maculopes, patches and erythematous papules partially hyperpigmented with

multiple multiples with scales in several places according to the clinical picture and predilection for maculopapular drug eruptions.

Investigation that can identify the causative agent of maculopapular drug eruption is drug patch test. The drug patch test works by eliciting a mild hypersensitivity reaction to the suspected drug when the drug is exposed to low concentrations (Fatangarea A, 2021); (Strazzula L et al, 2014). Based on the guidelines set by the European Society of Contact Dermatitis (ESCD) there are three important components that determine the success of the patch test, namely the time of implementation, the time of interpretation and the method of assessment. According to the guidelines issued by the ESCD, patch testing should be carried out within 6 weeks to 6 months after being free of lesions.20,21 The patch test result reading time recommended by the ESCD is 20 minutes after the chamber is opened on day 2 (48 hours), then The results were read again on day 3 (72 hours) and day 4 (96 hours). The method of assessing the patch test results according to the ESCD is as follows: (?+) for doubtful results; (+) for mild reaction, minimal erythema, infiltration and papules; (++) for strong reactions of erythema, infiltration, papules and vesicles; (+++) for very strong reaction, severe erythema (Wolf K et al, 2017); (Hoetzenecker W et al, 2015).

In this case, the patient underwent a patch test after six weeks of being free of lesions according to the ESCD guidelines. The results were read on the 2nd, 3rd and 4th days where negative results were obtained on all reading days. False negative results on patch tests can be influenced by several factors, including inadequate antigen penetration, inappropriate reading time, patch test sites previously applied with topical corticosteroids in less than 6 weeks, patch test sites exposed to sunlight, patients still taking oral corticosteroids, allergens not in active or degraded form, solid allergens such as cosmetics, wet or detached patch test areas, allergens tested are photosensitive but not exposed to irradiation, sweating, friction or pressure (Bras Dermatol. 2012). (Caplan A et al, 2019) In this case, a negative result was obtained on the patch test but there were no factors that could cause the above false negative result, but since the reading of the results on the 2nd day, the reactivation of the lesion was getting worse on the 3rd and 4th day. This is similar to the case reported by Cordoba et al. in 2016 in Spain where a drug patch test was carried out to identify the drug causing DRESS negative results on all days of reading the results, but reactivation of DRESS lesions was found on day 8 (Córdoba S et al. 2016); (Fatangarea A, 2021).

A study by Teo et al in 2007 in the UK reported reactivation of DRESS cases during patch testing of ranitidine, rifampin and vancomycin. Positive results were only obtained for ranitidine, but in vitro T cell examinations were positive for all three, so it was suspected that in vitro T cell examinations gave false positive results. At the time of provocation test for these three drugs, there was reactivation of the lesions after provocation of oral rifampin. The reactivation of the lesion in the patient after the patch test was strongly suspected to be caused by rifampin even though it gave a negative result on the

patch test. Reactivation of allergic drug eruptions after patch testing is rare and reactivation of maculopapular drug eruption lesions has not been reported (Fatangarea A, 2021); (Strazzula L et al, 2014) In this case, the negative results obtained in the patch test cannot be used as a reference and this result can be caused by the drug concentration being too low or because the maculopapular drug eruption itself is not triggered by the drug itself but its metabolites, however, absorption of the drug from the patch test alone is sufficient to cause reactivation.

Although the patch test in this case gave negative results for all allergens, suspicion of the drug being the causative agent can be identified based on the onset of disease where the maculopapular drug eruption usually occurs within one day to three weeks after drug ingestion with a peak incidence on the day to day. -9 (Wolff K et al, 2017); (Yunihastuti E, 2014) The patient in this case had been taking ticagrelor, ramipril, atorvastatin, furosemide, spironolactone, bisoprolol, acetylsalicylic acid as routine drugs for one year, while allopurinol was only taken for five days before the onset of the eruption and the patient denied a history of previous allopurinol consumption, so based on the onset of drug exposure. , allopurinol was strongly suspected as the causative agent and our patient was diagnosed with a maculopapular drug eruption et causa suspect allopurinol. Definitive identification of the causative agent that can be considered to be carried out includes examination of blood serum by ELISA or by LTT which can be done in vitro (Fatangarea A, 2021); (Wolf K et al, 2017); (Hoetzenecker W et al, 2015).

The main management of maculopapular drug eruptions is to stop suspected drug exposure, other therapies are supportive and symptomatic such as adequate nutrition, systemic therapy in the form of oral antihistamines to reduce itching and corticosteroids if the lesions are extensive.

Conclusion

A case of maculopapular et causa drug eruption with suspicion of allopurinol has been reported in a 56-year-old male patient. On dermatological examination of the facial region, the anterior trunk, posterior trunk, superior and inferior extremities bilaterally showed macules, erythematous patches and papules, some with multiple hyperpigmentation with scaling in several places. The patient was treated with discontinuation of the suspected drug, oral antihistamines, systemic corticosteroids, topical corticosteroids and emollients. After the patient was lesion-free for 6 weeks and fulfilled the requirements for the patch test, a patch test was performed but the results were negative in all chambers and the reactivation of the lesions since day 3 was suspected to be caused by allopurinol.

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