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Case Report

IDENTIFICATION AND TREATMENT OF ERYTHEMA MULTIFORME INDUCED BY ALLOPURINOL

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KEYWORDS

Allopurinol, erythema multiforme, identification, therapy

ABSTRACT

Introduction: Allopurinol is a xanthine oxidase inhibitor and has become established as the drug of choice for preventing and treating chronic gout. Erythema multiforme (EM) is an immune-mediated reaction that involves the skin and sometimes the mucosa. Many cases of EM are caused by drugs, one of which is allopurinol. The purpose of the case study is to explain the identification of allopurinol as a predisposing factor for EM and how it is treated.
Case: A 56-year-old woman came with complaints of scabs on her lips for 1 week ago, and had been treated with corticosteroid ointment for 3 days. Extraoral examination showed hemorrhagic crusts on the upper and lower lips with erosive surrounded by erythematous margins. On the extremity found a target lesion on the right hand. Based on the examination, the patient was diagnosed with Erythema Multiforme with a differential diagnosis of herpes labialis and herpes associated erythema multiforme.
Case Management: The therapy in this case was giving antihistamines for 1 week, NaCl 0.9% compresses on the lips for 30 minutes 3 times a day, after 2 weeks of treatment added with the application of 1% hydrocortisone cream as an anti-inflammatory and petroleum jelly on the lips as a moisturizer.
Conclusion: Identification of the etiology of this EM case was carried out through anamnesis and history of drugs consumed as well as administration of topical corticosteroids as anti-inflammatories and oral antihistamines to reduce allergic reactions.

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INTRODUCTION

Allopurinol and its main metabolite, oxypurinol, have a system of action that directly inhibits uric acid synthesis by inhibiting xanthine oxidase (oxidoreductase), which is an enzyme that catalyzes the conversion of purine hypoxanthine derivatives into xanthine and then xanthine into uric acid. Allopurinol is the primary therapy for treating chronic uric acid disorders, hyperuricemia associated with malignancy therapy, and kidney stones accompanied by hyperuricosuria.[1–4]

Erythema Multiforme (EM) is a condition mediated by the immune system that is self-limited or recurrent disease characterized by round erythematous papules with concentric color changes. The clinical features of EM often mimic those of other conditions such as Steven-Johnson Syndrome (SJS), but several clinical studies have concluded that EM and SJS are distinct disorders. Currently EM is associated with type 4 hypersensitivity reactions mediated by T lymphocytes and triggered by several predisposing factors. These include infection with herpes simplex virus (HSV 1 and HSV 2), drugs, malignancies, autoimmune disorders, radiotherapy and immunizations.[5–9]

Epidemiology of Erythema multiforme (EM) has very limited data because this disorder is an acute disorder. In addition, the EM classification is still not recognized and still overlaps to Steven-Johnson Syndrome and Toxic Epidermal Necrolysis. However, there is a study conducted by Samim, et al that the prevalence of EM occurs in less than 1% of all hypersensitivity reactions that occur. The age range for EM sufferers is around 20-40 years and it is more common in women than men with a ratio of 1.5:1.0. The recurrence rate of this disorder is up to 37% with a higher prevalence in certain Asians. Oral manifestations of EM vary widely, ranging from 35% to 65%, although the mortality rate of these cases has not been reported.[5,10]

One of the predisposing factors for the emergence of EM is drugs. Allopurinol is a drug which, according to several studies, is one of the drugs that most often triggers the appearance of EM. The exact pathogenesis of allopurinol-induced EM is still unclear, but several studies have concluded that it is related to a complex interaction of various factors including the presence of drug metabolism with the accumulation of the active metabolite of allopurinol, oxypurinol which can trigger a drug-specific T-cell response facilitated by genetic-HLA.[11] The aim of this case study was to identify and describe allopurinol-induced erythema multiforme therapy.

CASE

A 56-year-old woman came to RSGM Saraswati Denpasar with complaints of scabs on her upper and lower aunt since ± 1 week ago, before the appearance of scabs, the patient took allopurinol obtained from the primary health care with complaints of gout. The day after consuming allopurinol, the patient's lips began to experience soreness, pain and canker sores began to appear which then dried to form scabs. The patient then checked the complaint at the primary health care and was given antihistamines and compresses with antiseptics. Because she felt that there had been no change after examining the complaint, the patient then checked the complaint to the dentist and was given 0.1% triamcinolone acetonide.

Based on extra oral examination, yellowish hemorrhagic and serous crusts were found on the upper and lower lips accompanied by erosive lesions on the lower lip and corners of the lips bilaterally, conjunctiva redness, non-icteric sclera, and lesions resembling atypical target lesions on the patient's right arm. Examination of the lymph nodes showed a palpable and painful submandibular gland, and no palpable and painless submandibular and cervical glands. Extra oral clinical picture as shown in Figure 1.

Intra oral examination revealed erosive lesions on the buccal mucosa and some parts of the tongue with white plaques on the dorsum of the tongue. Intraoral assessment cannot be carried out optimally because the patient has difficulty opening his mouth. Based on subjective and objective examinations, it is recommended to do a complete blood count and anti-HSV 1 IgG serological examination because there is a suspicion of viral

involvement in this case. The results of blood tests and serology are in Table 1.

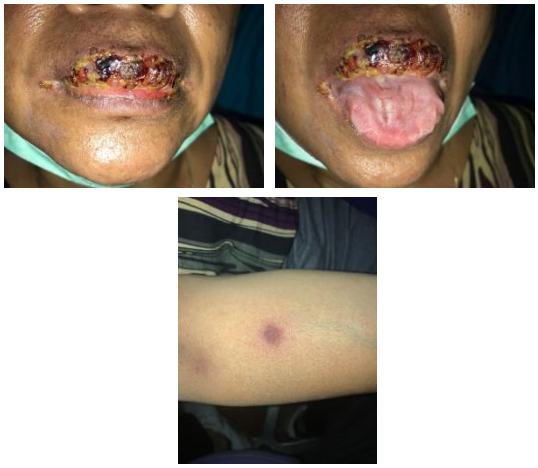

Figure 1. Hemorrhagic crust with erosive upper and lower lip at the first visit also atypical target lesion on right arm.

Table 1. Hematological and Serological examination

Examination	Result	Reference Value	Unit
Hemoglobin	12,6	11,7-16,0	g/dL
Erythrocyte	4,35	3,80-5,30	10^4/µL
Hematocrits	39	35-47	%
MCV	89	81-101	fL
MCH	29	27-34	pg/cell
MCHC	32	31-36	g/dL
RDW	12,0	11,5-14,5	%
Leucocytes	10.030	3.600-10.600	/µL
Eosinophils	2	0-3	%
Basophils	0	0-2	%
Stem Neutrophils	0	3-5	%
Segmental Neutrophils	68	50-70	%
Lymphocyte	26	18-42	%
Monocytes	4	2-11	%
Thrombocyte	464.000^H	150.000-450.000	/µL
ESR	35^H	0-30	mm/hour
Immunology			
IgG HSV 1	Negative: 3,8	Negative: < 20 U/mL Borderline: 20-25U/mL Positive: >325U/mL	

H: High, L: Low

Based on subjective and objective examinations accompanied by supporting examinations, the patient was diagnosed with Allopurinol-induced Erythema Multiforme by eliminating the suspicion of HSV 1 virus involvement because the results of anti HSV 1 IgG serological examination showed negative results in the patient.

CASE MANAGEMENT

Based on the diagnosis of the case above, for pharmacological therapy the patient was instructed to continue using antihistamines, while the oral disease department gave NaCl 0.9% compresses compressed with sterile gauze for 30 minutes 3 times a day. Apart from that, the provision of antiseptic Chlorhexidine digluconate 0.12% mouthwash to maintain the patient's oral hygiene and multivitamins as supportive therapy in this case.

After one week, at the second visit, complaints of sore lips had subsided, extra oral examination showed hemorrhagic crusts that had dried up and looked black. Intraoral conditions, erosive lesions have improved (as shown in figure 2). Patients were instructed to keep compressing their lips using NaCl 0.9% and keep taking multivitamins. Chlorhexidine digluconate 0.12% mouthwash was continued and the antihistamine was discontinued.

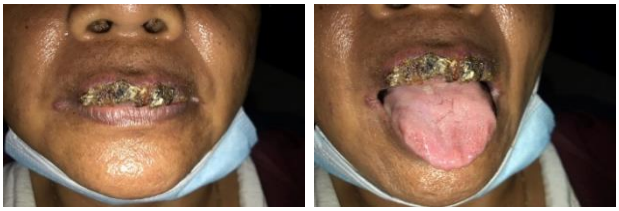

Figure 2. Hemorrhagic Crust had dried up.

On the third visit, 2 weeks after the first visit, there were no complaints of sore lips and the entire oral cavity. Extraoral examination showed no hemorrhagic crusts and only black macules were left. Intraoral examination showed no abnormalities (as in figure 3). Subsequent therapy, the patient was instructed to apply 1% hydrocortisone cream twice a day for one week. The use of NaCl 0.9% compresses was discontinued. The patient was instructed to come back 1 week later.

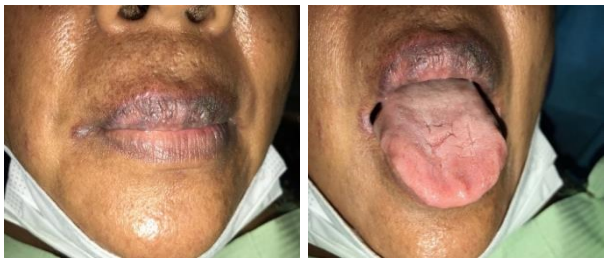

Figure 3. Hemorrhagic crusts have peeled off and left blackish macules

On the fourth visit, the patient had no complaints and was able to eat and drink well. Extraoral examination showed that the lips were still dry. Hydrocortisone cream 1% is used according to the instructions. The next treatment is applying petroleum jelly to dry lips. Hydrocortisone cream 1% was discontinued. Figure 4 shows the condition of the lips that have been applied petroleum jelly.

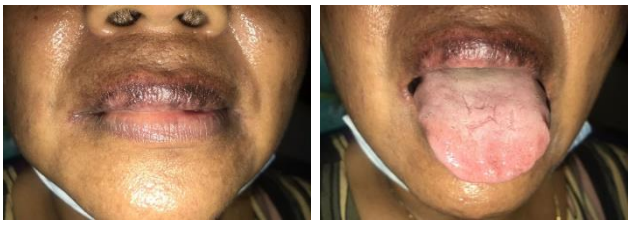

Figure 4. condition of the lips that have been applied petroleum jelly

DISCUSSION

Adverse drug reactions can be classified into 2 types, Type A which is a reaction to drugs that are predicted to trigger a drug reaction, and Type B which is a reaction related to genetic abnormality and immunological hypersensitivity that appears depending on the dose of the drug administered into the body. Hypersensitivity reactions to allopurinol have a prevalence of approximately 2% of all patients. Recent studies have shown that there is a very strong association with the reaction of the HLA_B*58:01 allele. Allopurinol has a mechanism of action rapidly metabolized by xanthine oxidase (XO) to oxypurinol with a half-life of 1-2 hours. Then oxypurinol is excreted by the kidneys with a half-life of about 15 hours. Previous studies suggest that oxypurinol has a role in immune-mediated allopurinol hypersensitivity reactions.[2,4,12,13]

The mechanism of the hypersensitivity reaction is still not clearly understood. However, several previous studies suggested that there was an immunological hypersensitivity reaction with CD8+ T lymphocytes, in the epithelium, inducing apoptosis of scattered keratinocytes and causing necrosis of satellite cells. The linkage of exogenous factors in this hypersensitivity reaction triggers an immunologically related reaction that appears as vesicles on the sub and intra epithelium.[12,14] Erythema multiforme (EM) is a mucocutaneous disorder which can also affect the oral mucosa which is usually triggered by viruses, drugs and other diseases. EM has a clinical picture in the form of a target lesion with different colors. Prodromal symptoms of EM are usually absent. The lesions usually appear within 72 hours of exposure to the patient and in some cases may cause mild pruritus or a burning sensation. As well as starting to appear erythema on the lips and buccal mucosa and erythematous macules which quickly experience necrosis in the middle accompanied by vesicles which then rupture to form erosive lesions.[8,12,15,16]

Although a standard procedure for validating an etiology of EM does not exist, the history of recent drug use from the patient's history is the strongest evidence in identifying causal factors for this disorder. Identification of this drug reaction is based on estimation and evaluation of probabilities.[15] Identification of Erythema multiforme induced by allopurinol to this patient can be done through anamnesis, history of consumption of previous drugs. However, a total IgE examination and patch test were not carried out because the patient refused to take this test.

Acute erythema multiforme (EM) is generally self-limited, requiring no treatment. According to Soares et al in 2021 who summarized Erythema multforme therapies based on the severity of EM. For acute EM as the first line, it is treated with topical corticosteroids, topical antiseptics and oral antihistamines, while for EM with mucosal involvement it is treated with high potency gel corticosteroids, oral antiseptics or anesthetic solutions, and for recurrent EM it is treated with antivirals because recurrent EM is more often triggered by viral infections.[8,17]

In this case the therapy given was NaCl 0.9% compress on the lips for 30 minutes. Compresses with NaCl 0.9% solution can reduce symptoms of edema due to the ability of NaCl 0.9% solution to draw fluid from the lesion by osmosis and has an anti-inflammatory response that reduces pain and erythema in the lesion. Mechanism of NaCl 0.9% solution in the treatment of lesions on the lips as a moist wound healing which has a moisturizing principle.[18,19] In addition, the pharmacological therapy given includes anti-allergy, hydrocortisone 1% cream, multivitamins also chlorhexidine digluconate 0,12% mouthwash for oral hygiene. Cetirizine is one of the most common antihistamines given for allergic reactions including acute food allergies, allergic rhinitis, and spontaneous chronic urticaria. Antihistamines were previously considered as histamine receptor antagonists, but have been reclassified as inverse agonists having affinity for G-protein coupled histamine receptors bound, thereby restoring cellular balance and reducing allergic effects.[20] Hydrocortisone is the main glucocorticoid secreted by the adrenal cortex. Hydrocortisone is used topically with the aim of being an anti-inflammatory which can suppress the clinical manifestations of certain disorders where inflammation is the most prominent clinical feature.[21] NaCl 0.9% compress therapy with 1% hydrocortisone was carried out in stages. Hydrocortisone 1% was applied to the patient's lips after the hemorrhagic crusts on the upper and lower lips had peeled off.

CONCLUSION

Identification of the etiology of this EM case was carried out through anamnesis and history of drugs consumed as well as administration of topical corticosteroids as anti-inflammatories and oral antihistamines to reduce allergic reactions.

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