Case Report

Amlodipine-induced lichenoid drug eruption: A case report

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Abstract

Lichenoid drug eruption is a rare side effect which may occur following administration of several types of medication. The pathogenesis of lichenoid drug eruption is postulated to be due to persistent activation of CD8 T lymphocytes against epidermal cells. There were only a few cases of Amlodipine-induced lichenoid drug eruption reported in literature. Due to the rare occurrence, this disease might be overlooked and lead to delayed diagnosis and treatment. It is vital for the attending medical practitioner to be able to diagnose this disease as amlodipine was found to be the most utilised medication used in Malaysia according to the latest Malaysian Statistics on Medicine 2015-2016.We report a rare case of a 60-year-old Chinese gentleman who presented with predominant oral lesions as well as cutaneous lesions after initiation of amlodipine. A diagnosis of amlodipine-induced lichenoid drug eruption was made after thorough assessment and evaluation.

Keywords: Amlodipine; drug eruptions; lichenoid eruptions; lichen planus, oral

Bangladesh Journal of Medical Science Vol. 22 No. 01 January'23 Page : 229-233
DOI: https://doi.org/10.3329/bjms.v22i1.61853

Introduction

Lichenoid drug eruption (LDE) is a rare type of cutaneous drug-induced adverse reaction associated with a wide variety of medications. Drugs that are associated with LDE include but are not limited to gold, antimalarial agents, antihypertensive agents and penicillamine.[1] LDE which resembles idiopathic lichen planus may involve cutaneous manifestation, oral mucosa, or both sites. Oral lichenoid drug eruption (OLDE) is less common than cutaneous lichenoid drug eruption (CLDE).[2]OLDE may manifest as linear or reticular pattern where there is a network of bluish-white elevations (Wickham striae) on the oral mucosa or atrophic and ulcerative lesions.[2]CLDE presents with symmetrical flat-topped, erythematous or violaceous papules which resembles idiopathic lichen planus on the trunk and extremities.[1] The commonest antihypertensive drug group causing adverse cutaneous drug reaction is beta blockers, of which atenolol is the commonest offending drug, followed by calcium channel blockers, of which amlodipine is the commonest offending drug.[3] To our best knowledge, there were 2 case reports that report

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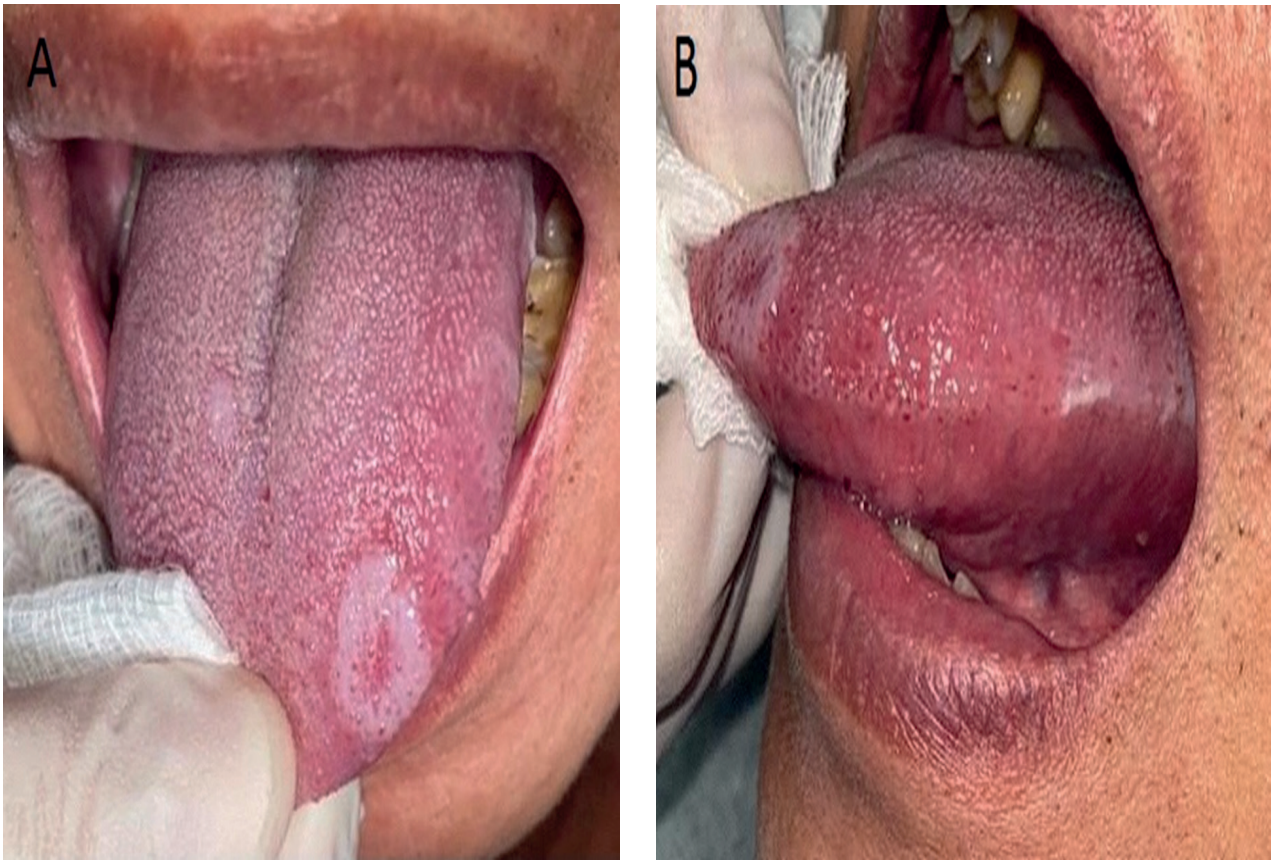

Figure 1A. Front view of white lesions with erythematous margins noted on left dorsal surface of the tongue; **B.** The same lesion from left lateral border of the tongue

on amlodipine-induced lichenoid drug eruption.[4,5] In the current case report, we present a 60-year-old gentleman with diabetes mellitus and hypertension who presented with oral and cutaneous lichenoid drug eruption after initiation of amlodipine.

Case report

Mr. LTS, a 60-year-old Chinese non-smoker businessman presented with multiple oral lesions on his tongue and right buccal mucosa for one-month duration. He also complained of pain and burning sensation over the areas of oral lesions while eating, especially when eating hot or spicy food. The lesions gradually increased in size. Otherwise, there were no associated numbness or loss of taste. He experienced difficulty to eat, however did not have weight loss or fever.

Patient had underlying type 2 diabetes mellitus on metformin 500mg BD for five years and his diabetes was well-controlled. Two weeks prior to the onset of symptoms, patient was started on amlodipine 10mg OD for hypertension as his blood pressure reading on two occasions were 162/92mmHg and 158/94mmHg respectively. He was not taking any other medications or traditional medications. Mr LTS also did not have drug allergy. He was a social drinker who consumed two to three cans of beer (2 units per can) twice a week. There was no family history of malignancy or skin disease.

On inspection, there were white lesions with erythematous margins noted on left dorsal surface of the tongue, left lateral border of the tongue (Figure 1), right ventral surface of the tongue as well as right buccal mucosa. Intraoral palpation did not reveal any induration or growth. There were no enlarged lymph nodes or salivary glands.

Several violaceous, flat-topped papules noted on lower third of his right leg. There were violaceous patches seen over bilateral dorsum of feet. Mr LTS's right elbow showed eczematous lesion over the lateral aspect. Upon further questioning, the patient revealed that these skin lesions occurred 3 days after the onset of oral symptoms. However, the skin lesions

were not pruritic and did not cause him concern. Other clinical examinations were normal.

Thus, OLDE likely caused by amlodipine was suspected. Amlodipine was discontinued and patient was started on perindopril 4mg OD. Betamethasone valerate cream 0.025% was also prescribed to him.

Mr LTS was referred to oral surgery department for evaluation and management of oral lesions. Incisional biopsy was taken at right buccal mucosa and left lateral border of the tongue. He was treated with dexamethasone mouthwash which involved crushing a 2mg dexamethasone tablet and mix with 25ml water then used as mouth rinse three times a day for two weeks. Topical oral application with hyaluronic acid oral gel was to be applied three times a day. Patient was also advised to avoid alcohol and spicy food.

Histopathological examination of right buccal mucosa showed surface mucosal covering of hyperparakeratotic and acanthotic stratified squamous epithelium. The epithelium showed irregular rete ridges with evidence of basal cell layer liquefaction. Occasional civatte bodies were seen at the basal membrane. Dense "band-like" lymphoplasmacytic infiltration was seen at the subepithelial region. The pathological changes were consistent with oral lichen planus or lichenoid reaction. Histopathological findings of specimen obtained from left lateral border of the tongue revealed hyperkeratosis mucosa with no evidence of lichenoid features present. Based on these results, the diagnosis was determined as amlodipine-induced lichenoid drug eruption (AiLDE). This adverse drug reaction was 'Probable' as per The World Health Organization-Uppsala Monitoring Center(WHO-UMC) causality assessment system and was reported as such to the hospital pharmacy. Patient was counselled regarding the nature of the lesions.

Following withdrawal of Amlodipine, Mr LTS's skin lesions resolved after two months' duration and there was no recurrence. His blood pressure was subsequently well controlled with perindopril 4mg OD. For the oral lesions, patient was co-managed together with oral surgery team. After one week of treatment, Mr LTS's pain and burning sensation while eating subsided. The whitish oral lesions have also reduced after three months' duration. A written informed consent was taken from Mr LTS for publication of his case. This case has been reported to NPRA, Ministry of Health, Malaysia (Reporting ADR/AEFI) (npra.gov.my)

Discussion

Amlodipine-induced lichenoid drug eruption (AiLDE) was diagnosed on the basis of history, physical examination findings, temporal relationship between administration of amlodipine and onset of symptoms, histopathological findings and reasonable clinical response after withdrawal of amlodipine. AiLDE was 'Probable' according to the WHO-UMC causality assessment system.[6]The time interval between drug initiation and the development of OLDE is highly variable, ranging from weeks to months, averaging at 2-3 months.[7] Latent periods of up to a year was also reported. It is dependent on the type of drug given, dosage of the drug, patient's individual reaction and presence or absence of other medications.[8] In this case, a latent period of two weeks between initiation of amlodipine and symptom onset shows an apparent temporal relationship.

Among antihypertensive medications, angiotensin-converting enzyme inhibitors (ACE-I), thiazide diuretics and beta blockers are most commonly associated with LDE.[8] Grinspan's syndrome is a triad of oral lichen planus, T2DM and hypertension, where it was postulated to be iatrogenically induced by drug therapy for hypertension and T2DM.[9] There were 2 case reports of AiLDE found in existing literature.[4,5] Even though this is a rare occurrence, it is important to be able to identify this condition and discontinue the suspected medication, in this case amlodipine. Amlodipine isdrug of choice for hypertension treatment for a wide range of age categories and most often used due to its prolonged anti-hypertensive effect.[10]

The pathogenesis of LDE is due to persistent activation of CD8 autocytotoxic T lymphocytes against epidermal cells. The cells which are primed from previous antigens persist at mucosal site as well and cause mucosal damage.[1]

This patient's site of OLDE at the buccal mucosa is one of the common sites of predilection. Other common areas in the oral cavity include tongue, floor of mouth, palate and alveolar ridges. According to Jacobson et al, OLDEs are likely unilateral and significantly associated with presence of basal cell

cytoplasmic antibodies.[11] This patient does not have dental restorative material such as amalgam filling whichis commonly associated with OLDE.[12,13] Differential diagnosis for the oral lesions include oral lichen planus, mucous membrane pemphigoid, chronic graft-versus-host disease, discoid lupus erythematosus, chronic ulcerative stomatitis and oral dysplasia.[7] CLDE is less likely to involve flexural areas when compared with idiopathic lichen planus. Wickham striae of the skin is also less commonly found in LDE.[1] All these points suggest LDE rather than idiopathic lichen planus.

The diagnosis of OLDE is based on clinical characteristics and histological findings based on modified WHO diagnostic criteria.[14] Histopathological findings of basal cell layer liquefaction, "band-like" lymphoplasmacytic infiltration at the subepithelial region and absence of epithelial dysplasia are consistent with both OLDE and oral lichen planus. The most precise clue is the resolution of lesions following discontinuation of the offending agent. The patient's skin lesions resolved after amlodipine was discontinued. Oral lesions also reduced after 3 months but persisted. This may be caused by the patient's continued consumption of alcohol. Patient should be encouraged to discontinue alcohol consumption as there is a possibility of malignant transformation.[14] In fact, OLDEs carry a much higher risk of malignant transformation to squamous cell carcinoma (142-fold increase with p-value 0.044) than oral lichen planus (no increase).

Challenge tests are not recommended as re-exposure of a patient with drug eruption to the suspected drug can be dangerous. Topical provocation patch tests are safer but have a high false-negative rate.[8] These tests were not done for our case. Indirect immunofluorescence may be indicated for diagnosis of LDE. Circulating antibodies reactive with basal cells of the skin will give rise to an annular fluorescence pattern otherwise called as 'string of pearls' reaction found in cutaneous drug reactions.[15] Indirect immunofluorescence test is negative in oral lichen planus.[7]

Treatment of LDE is first by identifying and discontinuing the culprit drug which leads to resolution of lesions in majority of cases.[8] Oral and cutaneous LDEs normally resolve within weeks or months after stopping culprit drug intake, however delayed responses may occur.[7]

Faint residual striations or mild erosive lesions in the oral cavity may persist following cessation of medication.[2] Topical corticosteroid use have been found to have variable success for OLDE where the causative drug cannot be discontinued due to patient's underlying clinical condition as well as for persistent residual lesions.[7] For our patient, dexamethasone mouth wash was used. Dexamethasone mouth wash was found to improve clinical outcome for OLDEs in a randomized cross-over trial.[16-18]

Topical corticosteroid is recommended for widespread CLDE.[1] For our patient, Betamethasone valerate cream 0.025% was prescribed. Systemic corticosteroids showed moderate success in certain cases where topical steroid use did not improve skin eruptions.[1]

OLDE may have premalignant potential as it has a much higher risk of malignant transformation than oral lichen planus.[14] It was suggested by this study to follow-up the patients once every six months for early detection of possible malignant transformation.[14] Carcinogens such as alcohol and tobacco products should be reduced or eliminated completely. In this case, advice was given to patient to discontinue drinking alcohol. As with advice for patients with oral lichen planus, spicy and hot food which may exacerbate recurrence of oral lesions should be avoided.[7]

AiLDE is one of the diseases that physicians should suspect when a patient presents with these lesions. Although rare, it is an important differential diagnosis as amlodipine is the most utilised drug in Malaysia with 63.4048 defined daily dose/1000 inhabitants/day in 2016.[19] The variable latent period between introduction of a new drug to symptom manifestation requires physicians to enquire extensively about drug history. Patients who have multiple comorbidities and are on multiple medications may complicate this further. However, once diagnosed, prompt discontinuation of amlodipine will lead to symptom resolution in majority of cases.

Disclosure of funding: None

Conflict of interest: No potential conflict of interest relevant to this article was reported.

Ethical clearance: Ethical approval not required. The patient's permission was obtained.

Authors contribution

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Acknowledgments

Special thanks to patient who consented his case for this publication.

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