Oral lichenoid reaction to herbal medicine: a case report

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Abstract

Lichenoid drug reaction is clinically and histopathologically similar to oral lichen planus, making differential diagnosis difficult. The most accepted criteria are based on the observation of improvement or disappearance of the lesions after withdrawal of medication in combination with their recurrence when the medication is reintroduced. A 44-year-old Thai male presented with a one week history of itching and burning sensation evolving from a white patch lesion on the dorsal tongue. Current medications were herbal medicines for his hairy tongue and azithromycin for his sore throat. The history, clinical findings, histopathological study of a band-like lymphocytic filtration with cytoid bodies, and disappearance of the lesions after withdrawal of medication confirmed the oral lichenoid drug reaction. We consider that this is an unusual case of oral lichenoid drug reaction triggered by herbal medication. The lesion persist for a long period following drug withdrawal.

Keywords: *lichenoid reaction, herbal medicine, lichen planus, oral*

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1. Introduction

Oral manifestations of drug reactions may be white, erythematous, vesicular, or ulcerative. They may also mimic oral lichen planus (OLP), in which case they are known as oral lichenoid reaction (OLR). However, their management is unlike that of OLP [1]. It was first mentioned in 1929. Since then, various drugs have been associated with the lesions [2,3]. There are neither specific tests to diagnose LDR nor specific tests for accountable drug; the most accepted criteria are based on the observation of resolution or disappearance of the lesions after discontinuing medication in combination with the recurrence of that lesion when medication is reintroduced [1,4]. The latter issue on rechallenge raises ethical issues [3]. In addition to systemic medication, lichenoid reaction can be associated with dental materials (i.e. amalgam, composite, gold, cobalt, copper, chromium, mercury, beryllium, nickel, palladium, silver, tin, composite, glass ionomer, porcelain), dental adhesives (acrylate compounds, eugenol) and food or flavoring agents (i.e. balsam of Peru, cinnamon, cinnamic aldehyde, eugenol, menthol, peppermint, vanillin). These characteristics are known under the name of OLR associated with dental materials.

The pathogenesis of drug reactions may be related to either immunologic (allergic reaction) or non immunologic mechanisms (toxic reaction, mechanic or galvanic attacked from mercury) [1,3]. For immunologic mechanisms, the reactions may be triggered by an antigenic component on the drug molecule, resulting in a hyperimmune response. Mechanisms include histamine release, immunoglobulin E (IgE)–mediated reactions, circulation of antigen (drug)-antibody complexes, and cytotoxic drug reactions. For non-immunologic mechanisms, those exogenous antigens may directly trigger mast cells, which then release their chemical mediators causing pathological keratinocyte apoptosis [5]. Somehow, the cytotoxic drug reactions produce the LDR. Under light microscopy, cells that have isolated keratinocyte apoptosis (cytoid bodies) can be found in either LDR or OLP. In a different way, an OLP response may occur to an endogenous antigen (abnormal recognition and expression of basal keratinocytes of epithelium) as an autoimmune-mediated disease where mast cells are secondarily engaged to the affected tissue through mediators released from T cytotoxic cells. It's likely that a cell-mediated immune response involving Langerhans cells and infiltrating cells composed of CD8+ T cells trigger the apoptosis of oral epithelial cells, especially in late lesions [1,2,5,6]. This information may also explain the different therapeutic approaches toward these two lesions [5], and why the cytoid bodies are mostly discover remarkable in OLP.

To establish diagnosis, the clinical appearances of OLP may provide sufficient information, in particular for the classic reticular form, which appears as interlacing white striae appearing bilaterally on the posterior buccal mucosa [1,4]. OLR associated with dental materials can be identified when the lesions are in close contact or proximity to materials (within 1 cm) [3]. These lesions are often localized and asymmetrical in distribution [7]. OLR associated with drugs are usually unilateral in distribution, and conform to the history of taking new drugs [1,4,8-10]. Compared

to lichenoid drug eruption (LDE), the latent period of lichenoid drug reaction tends to be longer. In addition, the drug can trigger the eruption, which eventually will not regress, even after its withdrawal. It is seen most commonly on the buccal mucosa (inside cheeks) but also on the tongue, floor of mouth, palate or gums. The changes may be noticed coincidentally with stinging/burning with hot or spicy foods or a roughness. There may also be a lichenoid drug eruption on the skin. The widespread ulcers typical of erythema multiforme are often representative of the other forms drug reaction [11]. Biopsy for the lichenoid reaction is optional when the lesion does not present with those typical clinical characteristics or when there is concern for possible malignancy [1,12). Otherwise, cutaneous patch test can be valuable for LDR; however the allergen selection and interpretation are controversial [13]. Differential diagnosis can take account of cheek biting, frictional keratosis, leukoplakia, lupus erythematosus, pemphigus, mucus membrane pemphigoid, erythematous candidiasis and chronic ulcerative stomatitis [4,15]. Unfortunately, histopathological findings are not sufficient for differentiation between OLP and OLR because of histopathological similarities [4]. Although the biopsy findings may not be diagnostic, they are useful in ruling out those other diseases [12,15].

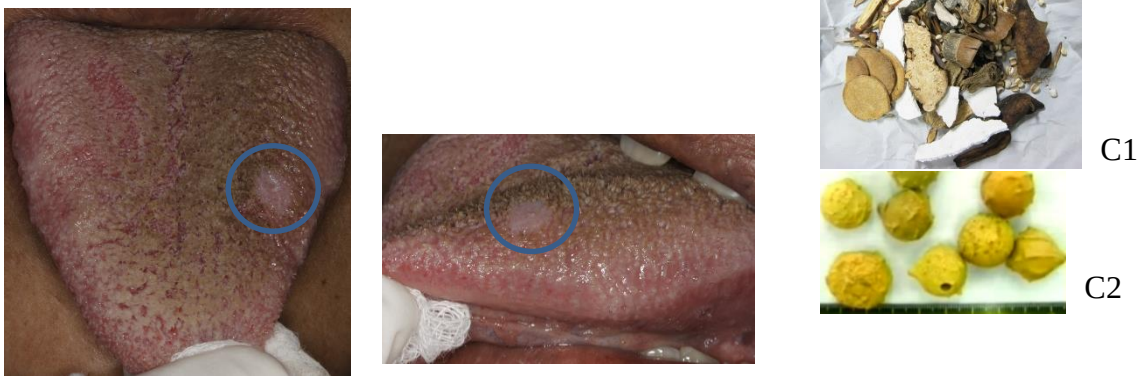
Currently, indirect immunofluorescence, a discrete annular fluorescence pattern from IgG staining represented at the basal cell layer of stratified epithelium may prove to be a suitable technique during evaluation of OLR [4,8]. The detection techniques of basal cell cytoplasmic antibody may be useful aide [4]. Eosinophil cell densities, distribution of Langerhans cells with CD1 and HLA-DR immunohistochemical markers, lichen planus-specific antigen, evaluation of mast cell counts [1,3,5,8]. However, the use of direct immunofluorescence techniques does not promise differentiation, because it is a T-cell-mediated disease in which there are no autoantibodies or other specific markers to identify [15]. The use of immunohistopathologic markers is also suggested for pathogenesis understanding in order to identify new diagnosis and therapy. Staining of mast cells with toluidine blue showed a difference in the ratio of degranulated to total mast cell counts in the reticular zone of the lamina propria, in which degranulated mast cells had a higher cell population in OLR than in OLP, and the difference was statistically significant. This method may be useful in differentiating OLP and OLR [5,14].

2. Case

The patient was thoroughly informed about his disease and the treatment he would receive. He agreed and gave his consent for the information. A 44-year-old Thai man visited the oral medicine clinic of the Dental Hospital, Faculty of Dentistry, Prince of Songkla University, Hatyai, Thailand, complaining of itching and burning sensation (symptomatology score, SS 5/10) related to white patch on the dorsum of his tongue for one week. Past medical history was hyperthyroidism with clinical of euthyroid status after treatment. He had no history of any previous drug allergy. He denied smoking, alcohol drinking, or betel nut chewing habits. Current medications were Chinese herbal medicine prescribed by traditional doctors

for his hairy tongue, azithromycin for his sore throat, and 0.1% triamcinolone acetonide (TA) paste to relief his soreness on the tongue prescribed by a pharmacist (Fig.1). Examination revealed a very mild white patch sized 2x5 mm without peripheral radiating striae on the left anterior dorsum tongue. Amalgam restoration was present on many teeth of all quadrants. There was no submandibular, submental or cervical lymphadenopathy. The perception for tastants of sweet, sour, salt, and bitter were normal in acuity. His Hb was 12.8 (12-16 g/dL), with a total leukocytes count of 6.39 (4.5-10x10^3/μL, neutrophil 50.6 (40-70%), lymphocytes 42.4 (20-50%), eosinophils 2.3 (1-6%), basophil 0.2 (0-1%), monocyte 4.5 (2-10%), ESR 60, (10-15 mm./h.) and his serum Zn level was 0.73 (0.7-1.5 mg/L). His unstimulated whole saliva flow rate was 0.3 ml/min (0.3-0.5 ml/min).

He was advised to discontinue 0.1 % TA paste and attend follow-up after one week. One week later, the lesion was prominently whitish and had increased in size to 5x9 mm but the sensation had decreased (SS 3/10). The tongue was coloured brown-black due to tannin staining from the application of a Benkanee topical application which was prescribed by a Thai traditional doctor to treat his hairy tongue (Fig. 1). A clinical differential diagnosis of candidal leukoplakia composed of LDR, lichenoid reaction associated with amalgam, and plaque type of OLP was made. We perform a cytological smear of the tongue with negative result for *Candida*. Based on the clinical impression, he was advised to stop taking herbal medicine; the lesion was totally excised and submitted for microscopic examination.



A B C1 C2

Fig. 1- Oral findings on visiting the oral medicine clinic and figure of the herbal medicine A: Frontal view (circle), B: Lateral view of tongue (circle), C1: the herbal medicine, C2: the Benkanee

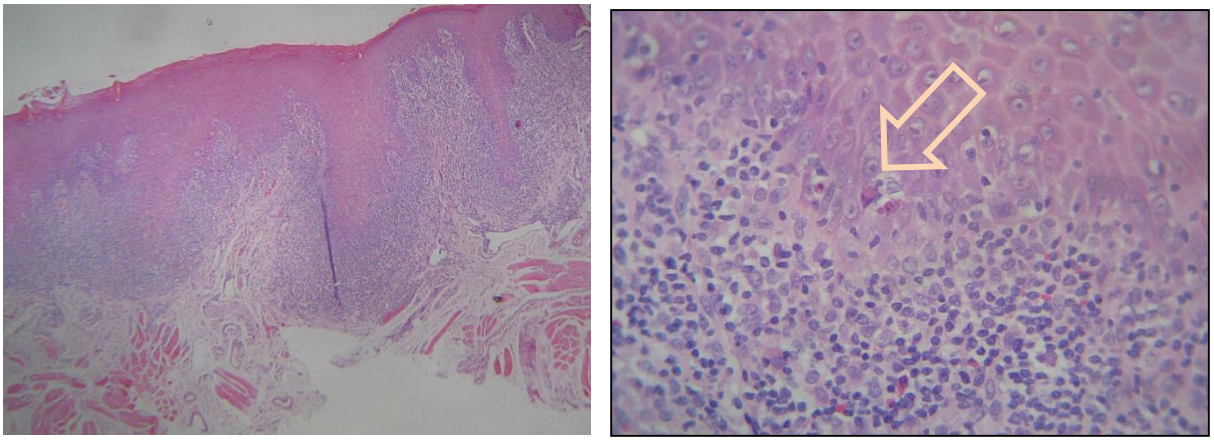
White patch sized 5x9 mm on 1/3 of the anterior at left side of the dorsal tongue could not be rubbed off. The tongue was coloured brown-black due to the application of a Benkanee tropical application. The black hairy tongue was noted.

A region section showed tongue mucosa with loss of tongue papillae in the central two third. The overlying epithelium was thinly squamous with hyperkeratinization. The rete pegs were elongated with a point-end and saw-tooth like appearance. A band-like infiltration of dense lymphohistiocytic cells around the rete processes was evident. Inflammatory infiltration of the basal and parabasal epithelial layers was present with few cytoid bodies. (Fig.2) Both the clinical diagnosis and the histological findings were consistent with the diagnosis of lichen planus or lichenoid reaction.

From the histological results, we started reviewing and paying attention to systemic diseases and current drug taken int the last 5 years, which may need to be excluded as a cause. The latent period from the beginning of administration of the drug to the appearance of the reaction was also considered. Prior to the appearance of the lesion, Chinese herbal medicine had been prescribed once a day for three days to cure spleen problem supposed to be caused by the patient's hairy tongue. After taking that herbal medicine, he developed an itching and burning sensation on the dorsal tongue on day 4, followed by a white lesion on the symptomatic area on day 5. On day 5, 0.1% triamcinolone acetonide (TA) paste to apply three times a day was prescribed by the pharmacist to relieve the patient's soreness on the tongue. 250 mg of azithromycin to be taken twice a day for five days also prescribed to relieve his sore throat

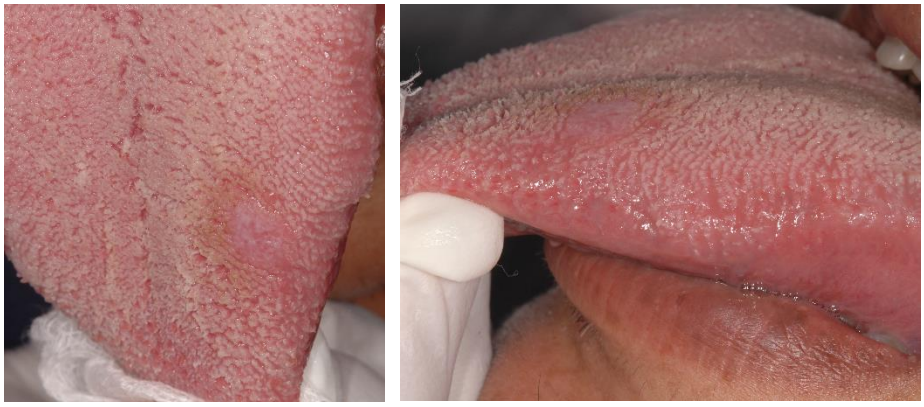
In the follow-up visiting, examination revealed a new emerging slightly white patch lesion after discontinuing all medicines for 1 month. Within another two weeks, that white patch had increased in size from 5x8 mm (Fig. 3) to 5x9 mm without any symptoms and he denied the history of taking of any new drug, food, or beverage. The treatment was reassurance and long-term follow-up every 2 weeks was planned. After discontinuing the offending drug for 3 months, the white lesion showed some improvement being paler in colour but still with the same size (5x9 mm). During this period, he was prescribed 20 mg of omeprazole by physician About 4 months after discontinuing the herbal medicine, the lesion completely disappeared (Fig.4), although he was prescribed 5 mg methimazole, and 10 mg propanolol by physician, for recurrent hyperthyroidism which lasted for 3 days. For thyroid investigations, the T3 was 286 (70-170 mg/dL), T4 was 2.53 (0.8-2 ng/nL), and TSH was < 0.004 (0.4-4 u/UmL). For definitive diagnosis, he was asked to rechallenge the offending drug but he refused. There were remaining normal mucosas represented in his cavity without any abnormal findings at the time of 6 months follow-up. For his hyperthyroid, the dose of antithyroid agent was reduced to 5 mg/day under physician prescription. The T4 was 1.07 (0.8-2 ng/nL), and TSH was 0.287 (0.4-4 u/UmL).

The diagnosis summary of the disease was as follows: the white patch of tongue lesion developed within one week with prodomal sign on day 4 after beginning Chinese medicine. The clinical findings exhibited significant resolution of tongue lesion until they disappeared after 4 months. There were no new lesions developing, which suggest the diagnosis of OLR (LDR or LDE) associated with Chinese herbal medicine.



A B

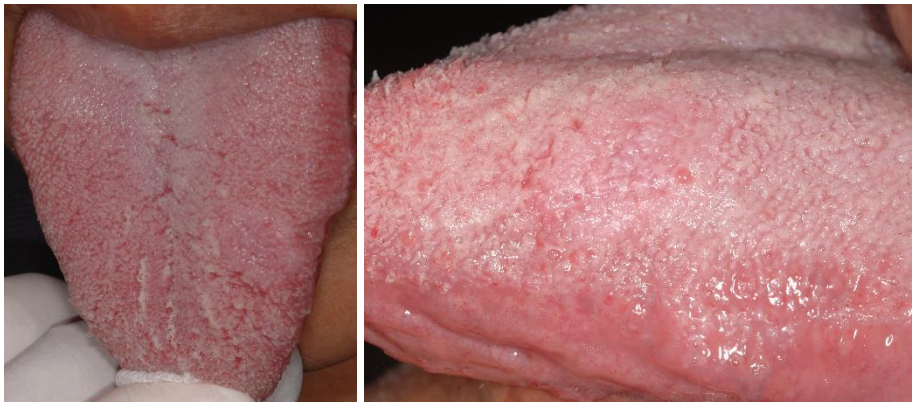
Figure 2: Biopsy specimen from tongue lesion A: showing hyperkeratotic squamous epithelium, elongated rete pegs with a point-end and saw-tooth like appearance, interface dense lymphohistiocytic infiltrate, B: showing inflammatory infiltration of the basal and parabasal epithelial layers with few cytoid bodies (transparent arrow)



A B

Fig. 3 - Oral findings 2 weeks after the excisional biopsy A: Frontal view, B: Lateral view of tongue

New emerging slight white patch lesion sized from 5x8 mm without any symptom



A B

Fig. 4 - Oral findings about 4 months after discontinuing herbal medicine A: Frontal view, B: Lateral view of tongue, no abnormal findings were observed in the oral cavity.

3. Discussion

Leukoplakia is listed and ranked first because it occurs more commonly in males aged above 35 years, frequently involves the tongue, and is not associated with any other local physical or chemical causative agents. Clinical findings of leukoplakia present as a white patch or plaque lesion that involves the oral mucosa, and cannot be removed by rubbing and cannot be classified as any other lesion [16,17]. The clinical distinguishing factors for differential diagnosis of LDR and an oral lichenoid reaction associated with amalgam comprise its atypical location, absence of bilateral symmetry, and presentation of old amalgam fillings. LDR was also considered because the patient had recently received systemic Chinese herbal medicine. Eventhough LDR tends to be unilateral [4,8-10], the most common sites of LDR involve the posterior buccal mucosa and lateral borders of the tongue [4]. OLP occurs mainly in females, in 1.9% of the population, and plaque type one is characterized as flattened white areas on dorsal surface of tongue resemble leukoplakia. However, the plaque type is less frequent and seldom present alone [4,18]; therefore, we placed OLP into the third rank.

The 4 basic tastants were performed because a number of studies have cited hyperthyroidism as a factor that may affect taste and burning sensation. In this patient, the taste responses for the 4 basic tastants were within normal range. Added together, the timing of the recurrent hyperthyroid well after presentation of the initial complaint and the fact that at that time the patient's hyperthyroidism was well controlled makes this an unlikely cause of the dysesthesia.

We performed total excision and submitted the tissue for routine light microscopy to investigate histopathology. Because the condition of the lesion itself it was not possible to identify the explanation clinically as the rapid increase in size which is smaller than 1 cm, and absent local factors. In addition, the clinical finding suggested plaque like OLP, for which it is recommended to receive a biopsy for ruling out dysplastic changes and leukoplakia [1]. Because our case was a white patch one, we did not submit the specimen for direct

immunofluorescence, which can aid in distinguishing cases of suspending vesiculo-bullous lesions [1,4] i.e. pemphigus vulgaris, mucous membrane pemphigoid, and erythema multiforme [4,12]. Serum evaluation for generic antinuclear antibodies and antibodies against double–stranded DNA and histone is often helpful for lupus like drug reaction [4], but nevertheless for ours.

The histological picture of our biopsy is consistent with both LDR and OLP. The histological criteria were well defined, being mainly a band-like lymphocytic infiltration in the most superficial zone of the connective tissue, with signs of degenerative liquefaction in the epithelial basal layer, and absence of epithelial dysplasia. Finding of cytoid bodies provides an additional feature for distinguishing LDR/OLP from leukoplakia [1]. Our histological findings may look like classical OLP because supportive histological characteristics for a lichenoid reaction include thin squamous basal cells with hyperkeratinization, infiltration of lymphohistiocytic cells around the rete processes, and the basal and parabasal epithelial layers present with few cytoid bodies. Normally, histopathological study of lichen planus shows hyperorthokeratosis, hyperparakeratosis, acanthosis with intercellular edema of the spinous layer. It also shows civatte (hyaline or cytoid) bodies in the spinous and basal cell layers and lamina propria which circulate antibodies binding to the cytoplasm of basal keratinocytes [8]. A saw-tooth appearance of the rete pegs was also seen. The submucosal leukocyte population is exclusively lymphocytic and specially limited to T cells without evidence of B or natural killer cells [4,6]. However, some reviewers have suggested that OLR may show deep as well as superficial T lymphocyte infiltrates rather than the classical band-like infiltrate of the lichen planus, and lichenoid lesions contain a diffuse cellular infiltrate consisting of lymphocytes, eosinophils and plasma cells.

To establish with complete criteria whether the Chinese herbal medicine was the cause of our patient's tongue lesion would require a rechallenge, or a provocative test with the offending drug. However, this should be undertaken only with the agreement of the patient and a medical counselor [1]. The ethical issues are questionable and the fear of the patient is a consideration. In our patient, a confirmatory rechallenging test was not performed because of patient preference and he was satisfied with the resolution. However, the significant disappearance of the oral lesion after discontinuous offending drugs completely suggests the diagnosis of OLR induced by Chinese herbal medicine.

The principle treatment of LDR and other types of lichenoid reaction is avoidance of the triggering factors (offending drugs or allergens), and ridding exposure to them. It may be problematic if it occurs in a situation of multiple, long-term drug usage [15]. Symptoms typically resolve quickly after elimination of the suspected drug or allergen [3,4,7,9,10,19-21]. However, in many cases, suspension of the medication may place the patient's health at risk, since the lesions may take 6 weeks up to 2 years to improve [20-21]. Although on average, it takes 1-2 months. The drug reaction will be slow to respond in case of a long-standing drug usage, and then a dentist should warn the patient that it may take up to 3 months to perceive clinical improvement [15]. This study, it took to disappear up to 4 months. In this condition, due evaluation of the risk/benefit ratio of suspending the medication is essential [1]. In the case where switching medication may not be an option in the management of this unwanted effect, it is recommended to

eliminate mechanical trauma, and maintain good oral hygiene. The pharmacological treatment of OLR is reserved for painful lesions as palliative care [4]. Antihistamines, corticosteroids, or dapsone [21,23,29,30] was used to inhibit autoimmune T lymphocytes responses for painful lesions and severe forms of atrophic and erosive lesions, since some offending drugs may take several months to resolve. Prednisone is a rational therapeutic choice, but in the lowest dose possible to maintain control of the reaction [15].

In our study, initiate with topical steroid application (0.1% TA paste) for 1 week did not lessen the patient's pain, in concordance with the report of Rice [20]. In fact, the complaint of pain sensation in our case can be abated and completely disappeared by itself after elimination of the offending drug within 1 week and 2 weeks, respectively. Fascinatingly, the reemergence of the tongue lesions after performing biopsy suggests a toxic response to the drug released or produced, and the exogenous compound may be covalently bounded into the affected cell membrane, or stimulated antibody production by the coupling of antibody to the antigen fixed to the cell membrane [15].

To determine lichenoid reaction associated with amalgam and curative treatment involves removing the amalgam restoration and using other dental materials as a substitute [1,4]. In our hospital, the number of patients with diagnosis of lichenoid reaction associated with dental materials (i.e. amalgam, cast alloy, and cobalt) has also been increasing.

In comparison to OLR, OLP has no curative treatment. Current treatments are palliative for symptomatic OLP, educated and reassurance for asymptomatic ones. Long-term monitoring of erosive and plaque-type form of OLP patients should be conducted considering the potential for malignant transformation [4,7,15,22]. In addition, OLP develops in a site of trauma (Koebner phenomenon) and is exacerbated by mechanical trauma, the biting/chewing, hard/crunchy eating, taking spicy/acidic/hot food and beverages, and smoking. Therefore, the exacerbation factors are all recommended to be eliminated. If an exacerbation occurs, the patient needs to request for an appointment to reinstitute the therapy [9,12,18].

Practically, drugs are administered for therapeutic purpose but drugs have also the potential to cause an unpleasant reaction. Some have a greater ability to do so than others [3,4]. In addition, some patients with a history of allergies have a greater tendency than others to react to drugs. For example, drugs that are thiol-like are more frequently accused (e.g. penicillamine, captropil). The lesions may occur concurrently with phenothiazine antipsychotic agents (lorazepam, lithium), tricyclic agents, and NSAIDs (aspirin, diflunisal, fenclofenac, ibuprofen, indomethacin, naproxen, rofecoxib, sunlindac and phenylbutazone) [3]. In many reports, these drugs are used in combination suggesting the likely presence of synergetic effects between those drugs. The following drugs can cause lichenoid drug reactions [1,3,4]: antimicrobial (tetracycline, dapsone, para-aminosalicylate, sulfamethoxazole, isoniazid, rifampin, streptomycin, mepacrine, and zidovudine) [23], antifungals (amphotericin B, ketoconazole), anti-parasitics (antimony compounds, organic arsenical, chloroquine and quinacrine), anti-hypertensives (ACE inhibitor, enalapril, atenolol, chlorothiazide, hydrochlorothiazide, labetol, mercurial diuretic, methyldopa, metroprolol, and practol,

and furosemide), anti-arthritics (aurothioglucose, colloidal gold, gold sodium thiomalate and gold sodium thiosulfate), chemotherapeutics (dactinomycin, imatinib), oral hypoglycemic agents of sulfonylurea type (chlorpropamide, glipizide, insulin, and tolbutamide), anticonvulsants (carbamazepine, oxcarbamazepine, phenytoin, and valproate sodium), antimalarials (chloroquine, hydroxychloroquine, quinidine sulfate, and quinine), miscellaneous drugs (bismuth, iodides, gold salts, interferon-α, and anti-TNFα [10], hepatitis B vaccine [19], and copper in dental casting alloy. Hence, for patients who have taken multiple suspect medications, the medication initiated most recently should be the target of a dechallenge.

Herbal therapy is gaining wider acceptance [24]. To expand the market for herbs, good management is necessary from the cultivation of herbal plants and the harvesting of herbs to the correct and hygienic way to store herbs to make them germ-free [25]. In Thailand, reports on allergic reactions to Thai herbal drug are very rare. In rare cases, Ta khrai (*Cymbopogon citratus*) essential oil has caused allergic reactions when applied to the skin. To minimize skin irritation, the oil should be diluted in an oil carrier such as safflower or sunflower seed oil before application. As with all essential oils, small amounts should be used only for a limited time. Somehow, many herbal medicines have been reported to cause fewer side effects when compared to modern medicine [26]. Up until now, it has been shown that 15 groups of symptoms of illnesses can be treated with the use of herbs instead of modern prescription drugs. These include medicine for the relief of pain, fever and allergies as well as for treatment of infection, diabetes, high cholesterol and even cancer. Common symptoms such as a headache, stomachache, joint pain, cramp and colds can be relieved by using a herbal remedy [24,26]. For Benkanee (Aleppo Oak, *Quercus infectoria* in family Fagaceae), the ethanol extract is common used to treat bacterial infection and also has an anti-inflammatory effect including antioxidant activities [27,28].

The patient's medical history may need to be revised, may need to be reviewed with attention to the appearance of systemic diseases and current drug taken related to time intervals, in order to exclude it as a cause [15]. The latent period from the beginning of administration of the drug to the appearance of the reaction is variable [4]; it may be weeks or years. A period of 2 months to 3 years has been reported for penicillamine, 2.5 years for 600 mg zidovudine [23], 1 month to 1 year for rofecoxib [29], 1 month for 40 mg anti-TNFα [10], 2-3 months for 400 mg imatinib [21,30], 3-6 months for ACE inhibitors, 4-6 weeks for quinacrine, 2 weeks for meoprolol [22], and 3 weeks after a third injection of hepatitis B vaccine [19]. In our patient, a period of 4 days passed between the initial medication and development of LDR. Thus, generally a thorough history of systemic medication use over the previous 12-24 months should be obtained.

4. Conclusion

The clinical suspicion of the presence of OLR was raised, and then an appropriate patient drug history of 2 years was conducted, after which the working diagnosis emphasized the suspicious drugs that may have cause OLR should be obtained. Carefully, the absence of immediate healing did not preclude an adverse drug reaction, as in unusual cases the lesion may persist for years following drug withdrawal. The appropriate manipulation was decided in conjunction with the patient's medicinal practitioner and oral medicine specialist.

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ไลเคนนอยด์ในช่องปากเหตุปฏิกิริยาจากยาสมุนไพร : รายงานผู้ป่วย

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บทคัดย่อ

ไลเคนนอยด์ในช่องปากเหตุปฏิกิริยาจากยามีลักษณะคลินิกและจุลพยาธิวิทยาเหมือนกับไลเคนเพลนัส ทำให้ยากต่อการวินิจฉัยแยกโรค เกณฑ์ที่ทำให้ทราบแน่ชัดมากที่สุดคือรอยโรคดีขึ้นหรือหายไปเมื่อหยุดใช้ยาและรอยโรคกลับเป็นซ้ำเมื่อมีการใช้ยาอีกครั้ง ชายไทยอายุ 44 ปี คันและแสบมาหนึ่งสัปดาห์พบรอยโรคสีขาวบนลิ้น ยาที่ผู้ป่วยรับประทานเป็นยาสมุนไพรเพื่อรักษาลิ้นเป็นขนและยาเอซิโทรมัยซินเพื่อรักษาอาการเจ็บคอ จากประวัติผลตรวจทางคลินิกผลทางจุลพยาธิวิทยาซึ่งมีลิมโฟซัยต์แทรกและเรียงตัวเป็นแถบพบร่วมกับซัยตอยด์บอดี รอยโรคหายไปเมื่อหยุดใช้ยาทำให้วินิจฉัยไลเคนนอยด์เหตุปฏิกิริยาจากยา ลักษณะที่พบไม่บ่อยในรายนี้คือไลเคนนอยด์เหตุปฏิกิริยาจากยาสมุนไพรเป็นแอนติเจน และรอยโรคคงอยู่นานหลังการหยุดการใช้ยา

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