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ORAL LICHEN PLANUS IN DRUG-RESISTANT PULMONARY TUBERCULOSIS PATIENT: A RARE CASE

(ORAL LICHEN PLANUS PADA PASIEN RESISTENSI-OBAT TUBERKULOSIS PARU: SEBUAH KASUS LANGKA)

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ABSTRACT

Drug-resistant pulmonary tuberculosis (DR-TB) is a hurdle in controlling pulmonary tuberculosis. The mucocutaneous tissues, including the oral mucosa, can be impacted by DR-TB medication, although infrequent. Highlighting Oral Lichen Planus (OLP) as a rare oral finding of drug side effects in DR-TB patients. Two male patients in DR-TB Clinic RSUD Tangerang City were referred to the Oral Medicine Clinic for complaints in the oral cavity. Treatment for DR-TB was given to the patient in months 8 and 11. The microscopic examination and sputum culture were negative when consulted. The patient denied any oral cavity complaints before being diagnosed with DR-TB. The intraoral clinical examination showed erosive lesions with a white keratinized plaque on the lips, buccal mucosa, labial mucosa, and tongue consistent with OLP. Pharmacological management involved using corticosteroids for mouthwash and lip ointment with

responsive results. Scheduled oral hygiene was also planned to eliminate focus infection in the oral cavity. OLP is a chronic inflammation of the oral mucosa mediated by immunological mechanisms and triggered by various agents. Drugs are one of the known triggers of OLP lesions. The findings of side effects in the oral mucosa tissue are believed to be a result of the DR-TB regimen of these two patients. Long-term drug use triggers the development of OLP in patients with DR-TB. OLP is an oral mucosa finding of drug side effects that is rarely reported in DR-TB patients.

Keywords: drug resistant; oral lichen planus; pulmonary tuberculosis

ABSTRAK

Tuberkulosis paru resisten obat (DR-TB) merupakan kendala dalam pengendalian tuberkulosis paru. Jaringan mukokutaneus, termasuk mukosa oral, dapat terpengaruh oleh obat DR-TB, meskipun jarang terjadi. Menyoroti Lichen Planus Oral (OLP) sebagai temuan oral langka akibat efek samping obat pada pasien DR-TB. Dua pasien laki-laki di Klinik DR-TB RSUD Kota Tangerang dirujuk ke Klinik Kedokteran Gigi untuk keluhan di dalam rongga mulut. Pengobatan DR-TB diberikan pada pasien pada bulan ke-8 dan ke-11. Pemeriksaan mikroskopis dan kultur sputum negatif saat konsultasi. Pasien membantah adanya keluhan di dalam rongga mulut sebelum didiagnosis DR-TB. Pemeriksaan klinis intraoral menunjukkan lesi erozif dengan plak keratin putih di bibir, mukosa bukal, mukosa labial, dan lidah sesuai dengan OLP. Manajemen farmakologis melibatkan penggunaan kortikosteroid untuk obat kumur dan salep bibir dengan hasil yang responsif. Perencanaan kebersihan mulut yang terjadwal juga direncanakan untuk menghilangkan fokus infeksi di dalam rongga mulut. OLP adalah peradangan kronis dari mukosa oral yang dimediasi oleh mekanisme imunologis dan dipicu oleh berbagai agen. Obat-obatan adalah salah satu pemicu yang diketahui untuk lesi OLP. Temuan efek samping pada jaringan mukosa oral diyakini sebagai hasil

dari regimen DR-TB dari kedua pasien ini. Penggunaan obat jangka panjang memicu perkembangan OLP pada pasien dengan DR-TB. OLP merupakan temuan mukosa oral akibat efek samping obat yang jarang dilaporkan pada pasien DR-TB.

***Kata kunci**: resisten obat; lichen planus oral; tuberculosis paru*

INTRODUCTION

Pulmonary Tuberculosis is still the most common cause of death worldwide, with around 10 million cases diagnosed in 2019. Up to 34% of all adult cases of TB in developing countries are due to the increasing prevalence of pulmonary TB.[1] The increasing number of pulmonary tuberculosis in Indonesia is also a significant challenge. Banten was included in the five provinces with the highest pulmonary TB in 2013.[2] This figure is also influenced by the increase in the number of drug-resistant pulmonary Tuberculosis (DR-TB). Indonesia is in the top 20 countries with the highest DR-TB cases. According to the World Health Organization (WHO), Indonesia is the fifth largest country that contributes to DR-TB in 2020.[3,4] So, the problem of DR-TB has become a global public health issue until now. DR-TB is usually associated with strong inactivity, high prevalence with severe mortality, long treatment periods, drug side effects that decrease quality of life, and expensive costs making it a challenge to treat successfully.[5] Patients with resistant pulmonary TB are typically given at least 5 anti-TB drugs over 20 months, which can lead to side effects.[6] Many side effects of DR-TB have been reported. 45% of patients experience moderate-to-severe adverse events as a result of the high incidence of side effects with these regimens.[7] Management of drug side effects is an important part of the success of Pulmonary Tuberculosis. However, side effects of DR-TB in the oral cavity are rarely reported.

Oral lichen planus is the most common chronic inflammatory oral mucosal disease that is linked to the cell-mediated immune response triggered by varied etiological agents.[8,9] The emergence

of oral lichen planus is often reported to be triggered by systemic medications, but there are only a few reports that OLP is triggered by DR-TB. There were difficulties in establishing the diagnosis and treatment for the lesions in both cases. Therefore, it is necessary to report the findings of oral lichen planus in DR-TB patients as a challenge in the successful treatment of pulmonary TB.

CASE REPORT

Two male patients in the DR-TB Clinic at RSUD Tangerang City were referred to the Oral Medicine Clinic for complaints in the oral cavity. The patient was given at least four anti-TB drugs to be taken for 20 months. (Table 1) They report experiencing pain, irritation, burning sensations, and taste disturbances. Both patients had a history of smoking, a low social and economic background, and poor therapy compliance. Patients were then consulted at the oral disease clinic with the information that the laboratory results showed improvements in blood components and that the microscopic examination and sputum culture were negative. Based on the history and the clinical appearance of the lesion, the presence of oral lichen planus was suspected. The diagnosis was made without histopathological examination because the patient refused a biopsy. Pharmacological management involved using corticosteroids for mouthwash and lip ointment with responsive results without stopping the DR-TB medication being administered. A scheduled oral hygiene program was also planned to eliminate focus infection in the oral cavity. The intra-oral examination also showed poor oral hygiene, generalized marginal gingival inflammation, and multiple teeth radix and pulp necrosis. However, the patient refused to have the focus of infection eliminated because they were worried that there would be risks after invasive procedures.

Table 1. Drug-resistant pulmonary tuberculosis medication

Case	Drug			
Case 1	Clofazimine	Linezolid	Cycloserine	Levofloxacin
Case 2	Clofazimine	Ethambutol	Cycloserine	Levofloxacin

Case 1

A 62-year-old male patient began treatment for drug-resistant pulmonary TB 11 months before oral complaints became apparent. He was diagnosed with drug-resistant pulmonary TB after a Rapid Molecular Test Method (TCM), which revealed that he had resisted rifampicin.

The patient is known to have no comorbidities. He complained that numbness in the hands and feet, insomnia, nausea, lack of appetite, and blurred vision began to appear after 2-4 months of DR-TB treatment. After 11 months of treatment, the patient began to complain of pain, irritation, burning sensations, and taste disturbances in the oral cavity. The patient denied any oral cavity complaints before being diagnosed with DR-TB.

The intraoral clinical examination showed erosive lesions and a white keratinized plaque symmetrical on the lips, buccal mucosa, labial mucosa, and tongue. The patient also had poor oral hygiene. The patient also reported a white appearance on the skin that felt thick and itchy. Compliance with treatment is a challenge in managing lesions in these patients. After several therapeutic evaluations, the patient said his oral complaints had improved. The plan to remove the focus of infection was rejected by the patient, even though he had been given information about the importance of this procedure.

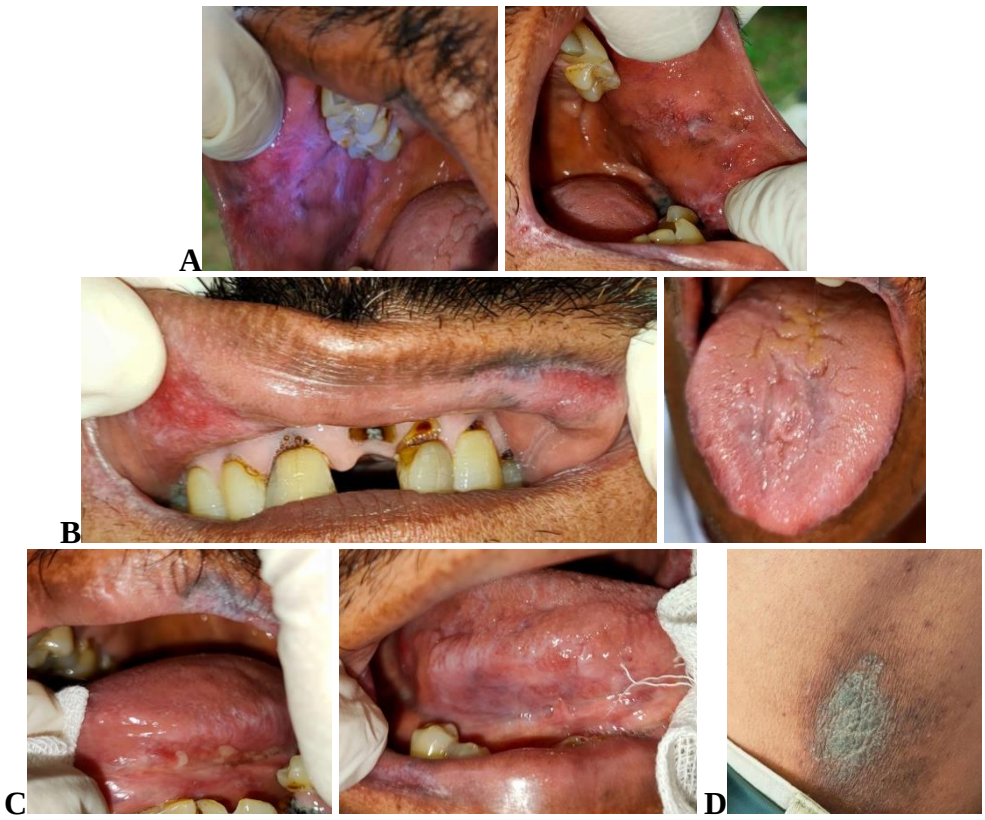

Figure 1. The clinical appearance of the first case lesions.
(A) The lesions on the buccal mucosa were bilateral and showed erosive lesions with a white keratinized plaque, **(B)**The lesions on the labial mucosa were bilateral and showed erosive lesions with a white keratinized plaque and fissure in the tongue dorsum with a white

keratinized plaque, **(C)**The lesions on ventral of the tongue were bilateral and showed erosive lesions with a white keratinized plaque, **(D)**The lesion on skin.

Case 2

A 44-year-old male patient experienced pulmonary TB treatment failure after undergoing category 1 pulmonary TB treatment for 6 months. After a Rapid Molecular Test Method (TCM) was carried out, the patient was declared rifampicin resistant. The patient has been known to have Diabetes Mellitus since last year. He began treatment for drug-resistant pulmonary TB 8 months before oral complaints apparent.

Complaints in the form of numbness in the hands and feet, nausea, lack of appetite, blurred vision, tinnitus, and skin pigmentation began to appear after 2-6 months of DR-TB treatment.

The intraoral clinical examination showed erosive lesions with a white keratinized plaque symmetrical on the lips, buccal mucosa, labial mucosa, tongue, and pigmentation on the lips. The patient had poor oral hygiene and bad compliance with treatment. He also refuses to eliminate the focus infection.

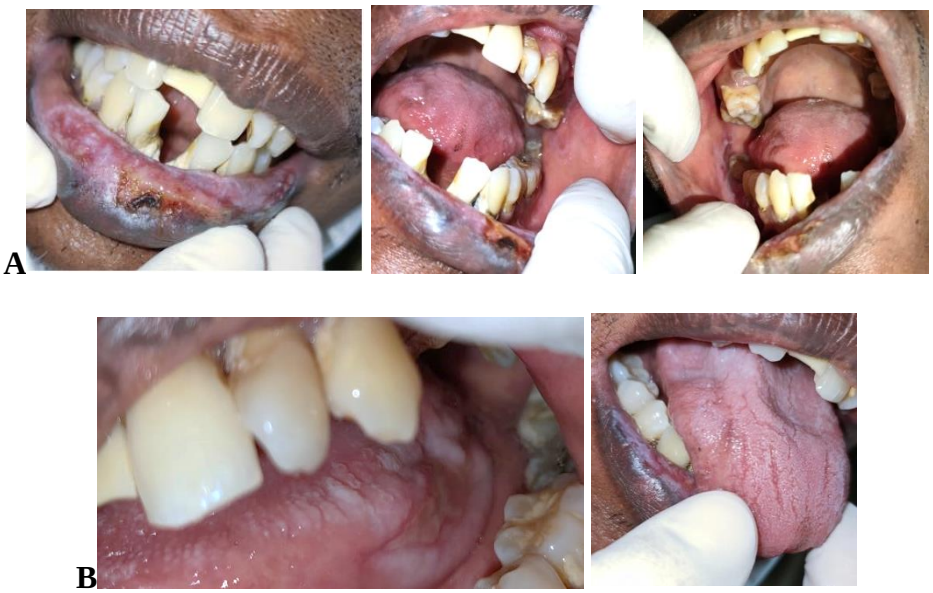

Figure 2. The clinical appearance of the second case lesions.
(A) The lesions on the buccal mucosa were bilateral and showed erosive lesions with a white keratinized plaque and erosive lesions with a white keratinized plaque in the lower lip, **(B)** The lesions on the lateral tongue were bilateral and showed erosive lesions with a white keratinized plaque.

DISCUSSION

The bacteria *Mycobacterium tuberculosis* is the cause of pulmonary tuberculosis, which is the most common infectious disease worldwide. The initial treatment for this disease is isoniazid and rifampicin. Nonetheless, the number of cases of resistance to these two drugs is on the rise every year. The rise in resistance to rifampicin is a significant danger, as it is estimated that approximately half a million people have been infected with strains that have higher mortality rates. The emergence and spread of rifampicin-resistant disease has posed significant challenges to pulmonary tuberculosis control and is threatening human health.[2,10,11,12] Both patients in this report were recorded as having low socioeconomic status. The risk of drug-resistant tuberculosis exposure is higher for individuals with lower economic status. A higher TB prevalence was observed in urban areas compared to rural areas, which may indicate the significance of sociodemographic conditions for TB prevalence. The last research found that poverty is also a contributor to the burden of tuberculosis. The emergence of infectious diseases, particularly the progression of tuberculosis to DR-TB, is linked to clean and healthy living habits.[3,4]

The drug resistance to rifampicin, which is the most effective drug for treating pulmonary TB, is present in both patients in this case. This is known from the results of examinations using the Rapid Molecular test method (TCM), which is generally carried out in health facilities in Indonesia to test pulmonary TB drug resistance. TCM is a renewal of the TB program for cases of drug-resistant TB. Due to its sensitive and specific nature, the TCM can detect simultaneously the bacteria *Mycobacterium Tuberculosis* and resistance to rifampicin. The use of TCM is limited to the diagnosis of TB and resistance to rifampicin quickly and accurately, and it is not suitable for monitoring or follow-up examination in patients who are undergoing treatment therapy. GeneXpert, a Catridge-Based Nucleic Acid Amplification Test (CBNAAT) is the currently used TCM tool recommended by the WHO.[13] However, the difference between these two patients is that the patient in the second case experienced failure of pulmonary TB treatment, which he had been undergoing for 6 months. Secondary resistance, or acquired resistance, is the term used to refer to the resistance that develops during TB therapy. The reason for resistance is either an inadequate regimen, incorrect use of the prescribed regimen, or other conditions. People who are exposed to and infected with resistant organisms are known as primary resistance. It is also known as the first-case patient.[2,8,10,14]

Unlike drug-susceptible tuberculosis (DS-TB) treatment, which only requires first-line antituberculosis, DR-TB treatment requires a combination of second-line antituberculosis drugs. The combination groups of anti-pulmonary TB drugs that were planned for 20 months were given to both of these patients. Levofloxacin, linezolid, clofazimine, ethambutol, and cycloserine were the medications available. WHO had recommended three groups of agents for DR-TB treatment. Group A includes levofloxacin and linezolid, while Group B includes clofazimine and cycloserine, and ethambutol is part of Group C. A combination of all drugs from group A and at least one drug from group B is recommended as a standard treatment for a long-term regimen that requires 18–24 months of therapy. Due to the prolonged duration, more complex, and more toxic regimens, DR-TB therapy can be quite challenging, with the likelihood of adverse drug reactions (ADRs).[15] A mixture of different groups of DR-TB medication agents was given to patients in both cases in this report for 20 months.

After 2–6 months of treatment, patients may experience systemic side effects. They complained of numbness in the hands and feet, insomnia, nausea, lack of appetite, blurred vision, lack of appetite, tinnitus, and skin pigmentation. Each of these drugs has different side effects. Side effects of DR-TB systemic medication that are often reported are heart health problems, kidney problems, electrolyte disorders, liver function disorders, vision problems, disorders of the digestive tract, nervous system, endocrine system, skin, muscles, bones, haematology, and hearing problems.[16] The side effects of DR-TB drugs can be mild, moderate, severe, or life-threatening. Complaints commonly reported by patients are nausea, vomiting, hearing loss, tingling in the fingers and toes, dizziness, psychological disorders, and skin pigmentation.[15] This is also what was conveyed by the two patients in this case report. The side effects complained of can be grouped into two parts, namely major and minor.[7]

The most important principle for managing side effects of drugs is early detection of side effects during treatment. These side effects must be quickly discovered, treated, and monitored. Side effects that appear and are complained about by patients should be recorded and a routine evaluation carried out. In evaluating the side effects of DR-TB drugs, their severity must also be assessed. Grade 1, or mild, refers to discomfort that lasts for more than 48 hours and usually does not require medical intervention or treatment.

Moderate severity Degree 2 is characterized by mild limitations in activities, which may require further examination but do not necessitate medical intervention or treatment. Grade 3, also known as severe severity, refers to a patient who has limited activity, requires medical intervention or light treatment, and may need hospitalization. In addition, there are side effects that can be life-threatening.[16] Drug-resistant tuberculosis (DR-TB) requires long-term and complex therapy that is associated with multiple adverse drug reactions. This can affect the patient's quality of life and behaviour regarding treatment.[15] It is crucial to schedule regular visits to the DR-TB clinic to activate and provide immediate treatment for any side effects that may arise. Routine visits are always scheduled for these two patients, but patient compliance is an obstacle to the success of this treatment.

Systemic medication used to treat DR-TB patients has been reported to have several side effects. Although there is minimal data on the side effects of DR-TB medication on oral mucosa, The author had difficulty finding references regarding OLP as one of the side effects of TB drugs in the oral cavity.

The clinical introduction of oral lichen planus was first made by Sir William James Erasmus Wilson in 1869, but it was histologically introduced by Dubdreuilh in 1906.[17] Oral lichen planus (OLP) is an inflammatory chronic disease of uncertain aetiology, although it is generally considered an immune-mediated disease that affects the mucous membranes and even the skin and nails. The lesion of OLP is believed to be a result of a cytotoxic reaction against the basal cells of the epithelium caused by a T cell (CD8) - mediated response. The pathological process involves the secretion of TNF-α and apoptosis of keratinocytes, as well as the secretion of chemokines that attract more proinflammatory cells to the lesion, resulting in chronic inflammation. Previously, there were 11 clinical types of OLP, but since 2016, the clinical types of OLP have been grouped into 6 types, namely erosive, plaque type, popular, reticular, atrophic, and blouse.[18,19] Cellular immunity can be induced by both endogenous and exogenous factors in genetically susceptible patients, and it appears that they play a significant role in the pathogenesis of OLP. Although the nature of the antigens involved in OLP is uncertain, several factors have been identified to cause OLP, including a systemic treatment. However, systemic drugs such as DR-TB medication are not widely reported to cause OLP.[20,21]

Usually, a complete history and typical clinical picture is enough to establish the diagnosis. The classic lesions of OLP can help establish a diagnosis based on clinical features (Wickham's striae, erythematous areas) alone. However, certain other lesions, such as lichenoid reaction, contact sensitivity, white sponge nevus, pemphigoid, and lupus erythematosus, show similar clinical characteristics, so it is necessary to carry out a histopathological examination. Lichenoid drug eruption does not exhibit classic Wickham striae, and commonly implicated drugs include gold, b-blockers, antimalarials, thiazide diuretics, and penicillamine. The lichenoid eruption caused by ethambutol and Pyrazinamide has been reported in a small number of cases in the literature, but none have been linked to mucosal involvement.[19,20,22] In cases of oral lichenoid drug eruption, it will respond to therapy if the suspected drug is stopped, in contrast to oral lichen planus, which can respond quickly to therapy without stopping the suspected drug. The oral lesions complained of healing quickly in both cases, even without stopping DR-TB medication.

The diagnosis is determined by the history and clinical and histopathological examination. The diagnosis accuracy is enhanced when skin lesions are present. Both lesional and normal-appearing areas should be present in marginal tissue during the biopsy. Due to the refusal of both patients, the two reported cases did not undergo a biopsy. However, the clinical picture of the oral mucosa shows the clinical characteristics of OLP. The skin disorder in the first case was identified to have the same lesion characteristics as the oral mucosa. This condition affects the skin, mucosa area, or both, where 40% of cutaneous lichen planus sufferers have oral mucosal lesions, 35% only have oral mucosal lesions, and around 25% only experience oral mucosal lesions. This condition most often occurs in adults and tends to occur in women.[19,20,22,23]

In 2013, Sahin and his team reported that lichen planus significantly increased the values of C-reactive protein, LDL cholesterol, and triglycerides, as well as affecting the dispersion of P waves on the electrocardiogram.[18] In these two cases, CRP, LDL cholesterol, triglycerides, and heart examinations were not carried out. In the second case, the patient had comorbid diabetes mellitus before undergoing DR-TB treatment. Diabetes mellitus patients are at great risk of developing active pulmonary TB due to changes in host cellular immunity. In 1963, Grinspan found an interesting association between oral lichen planus, diabetes mellitus, and hypertension,

which he termed Grinspan syndrome. The smoking habits of both patients could also be associated with the development of OLP cases, as reported in the Indian population.[20]

In general, OLP cases are not realized by the patient. Usually, patients start complaining of symptoms of roughness in the oral mucosa, burning sensations, and pain in the oral mucosa due to hot and spicy foods slowly. The appearance of red or white patches slowly progresses to the development of mouth ulcerations. The reticular form of oral lichen planus usually shows gross symptoms in contrast to the atrophic/erythematous and erosive/ulcerative forms, which show symptoms of a burning sensation, pain, and sensitivity to food spices. The patient mentioned that he had never experienced any mouth complaints at the start of DR-TB treatment. After 8 and 11 months of DR-TB treatment, both patients experienced oral cavity complaints. The lesions that appear are the three most common forms of OLP lesions, namely reticular, atrophy or erythematous, and erosive. The lesions are bilateral and seen on the buccal mucosa, mucobuccal folds, tongue, and lips. Even in the second case, pigmentation was found on the lips, where OLP lesions were generally also associated with uneven brown melanin deposits in the oral mucosa, which is referred to as inflammatory melanosis. In both patients, multiple teeth radix and calculus throughout the gingival area were also visible. Sharp remaining tooth roots can trigger OLP lesions in response to trauma from the sharp tip of the root. Poor oral hygiene and calculus accumulation can worsen OLP, which may be a result of Koebner's phenomenon.[20,24] The finding of a focus on infection in the form of root caries and tartar is part of chronic inflammation of the oral cavity, which could play a role in causing OLP or increasing the severity of OLP in DR-TB patients. This was reported in 1922 and 1936 in women with findings of skin OLP and LP, confirmed by streptococci and staphylococci in these lesions. So the conclusion was drawn that there was a suspected relationship between bacteria in the mouth and OLP.[18]

Practitioners are faced with a therapeutic challenge because OLP treatment is palliative and there are no curative treatments available. The goal of treatment is to control pain, signs, and symptoms. Local corticosteroids remain the first line of treatment. The physiological inhibition of inflammation is attributed to corticosteroids. The effectiveness and safety of corticosteroids in patients with severe inflammatory conditions have been demonstrated in several randomized

studies. Systemic corticosteroids should also be prescribed as a first-line treatment in severe and extensive forms of OLP or if resistance to local corticosteroid therapy occurs. In the event of contraindications to corticosteroid therapy or resistance to corticosteroid therapy, other drug treatments such as retinoids, tacrolimus, cyclosporine, and aloe vera can be utilized as a second-line therapy. If drug therapy fails, other treatments such as laser, withdrawal, and psychotherapy may be contemplated.[21,25] The advantage of using topical steroids is that they have fewer side effects compared to systemic administration. Side effects include candidiasis, thinning of the oral mucosa, and discomfort during application. Adrenal suppression can occur if topical formulations of more potent corticosteroids are used excessively for prolonged periods or with occlusive dressings. It is recommended to use the lowest-potency steroid that has been proven to be effective.[26] Maintaining good oral hygiene through effective oral hygiene control measures like scaling and oral hygiene instruction is essential, which can enhance the healing of the lesions and decrease also the painful symptoms of OLP.[20,27]

CONCLUSION

Many reports describe an increase in the incidence of DR-TB and an increase in cases of systemic side effects of DR-TB drugs, but this is not the case with side effects of DR-TB medication on the oral mucosa. Systemic medication that is used for a long period can frequently trigger OLP events. There are challenges in establishing a diagnosis of OLP lesions in cases of side effects of DR-TB medication, in this case, due to the absence of histopathology results as the gold standard for diagnosis.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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