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Case Report

An unusual case report of an early proliferative verrucous leukoplakia

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Abstract: Proliferative verrucous leukoplakia (PVL) is a very rare kind of leukoplakia with great risk of cancerization. The previously reported PVL are mostly elderly patients with a longer progress. We received one rare case of an early PVL patient. The early clinical manifestations, possible pathogenic factors, clinical monitoring and treatment methods were analyzed comprehensively.

Keywords: Early proliferative verrucous leukoplakia, laser therapy, low level laser therapy

Proliferative verrucous leukoplakia (PVL) is a rare potentially malignant lesion of oral mucous that firstly described by Hansen et al in 1985. PVL presents very specific characteristics, mainly a more aggressive biological behavior than any other forms of leukoplakia expressed by: A tendency of multiple occurrences, a high probability of recurrence and a high rate of malignant transformation [1]. Early detection and treatment may have important significance for PVL. However most cases diagnosed before were elderly women with long time course, clinically marked by significant multifocal keratoses [2]. Rare cases of early PVL are reported. So we report an infrequent case of early diagnosis of PVL in a young patient. A comprehensive analysis of its clinical features, possible causative factors, clinical monitoring and associated treatment options were also discussed.

Case presentation

A male patient, aged 30 years, attended the Department of Oral Medicine at Stomatological Hospital of Southern Medical University in August 2015, with the complaint of foreign sense of left lingual margin for 3 months. The patient has no history of treatment. On personal history, he reported of smoking since last 9-10 years. He used to take 1-2 packets/day. The patient was in a state of prolonged staying up for work. On clinical examination, an exophytic growth about 1 cm in diameter was seen at the posterior portion of left lingual margin. The surface was white with burr-like (**Figure 1**). The texture is soft and without tenderness. The lower and leading edge of the exophytic growth was scattered with irregular gray and white patches (**Figure 1**), and the quality is soft. There were no irritation factors such as sharp edge, bad restoration and so on in the corresponding tooth region. By combining the characteristics of oral lesion, a primary diagnosis of PVL was drawn. we proceeded initial treatment suggestions as follows: 1) quit smoking and try to avoid staying up late; 2) an overall physical examination was suggest to exclude any hidden disesse; 3) excision and histopathological examination was advised for the verrucous growth area of the posterior part of the tongue; 4) close surveillance was suggested for the irregular gray and white patches in anterior area of verrucous region. The patient underwent general physical examination and no obvious abnormality was observed. He then underwent resection and biopsy at our hospital in September 2015. A high energy of 980 nm diode laser (Hager & Werken GmbH & Co.KG, Germany) was used to cut exophytic verrucous lesion (continuous output mode, power 3 W). The excision included 3-5 mm of normal mucous surrounding the lesion. The depth of

Figure 1. A white exophytic growth about 1 cm in diameter was seen at the posterior portion of left lingual margin (A); There were scattered grey and white patches in front of the growth (B). Postoperative view of three weeks after the first biopsy (C).

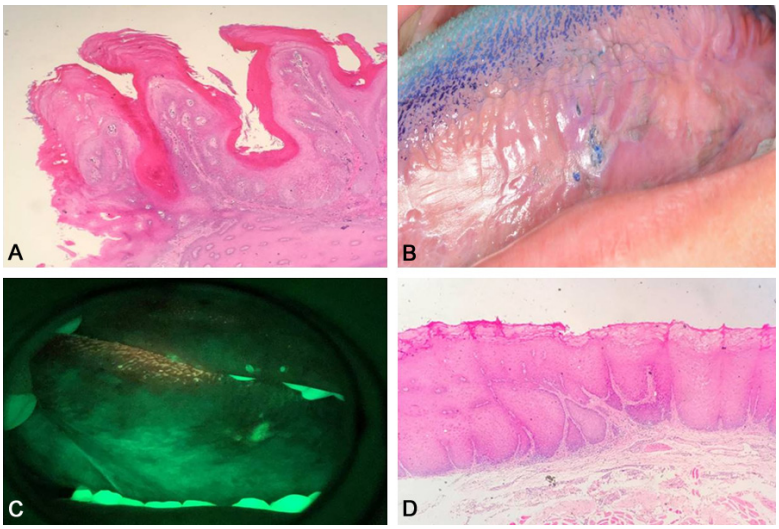

Figure 2. The first biopsy showed verrous hyperplasia with mild to moderate hyperplasia (A). (HE, original magnification × 40). There were some white plaque areas in front of the operated lesion with positive TBlue staining (B), accompanied by loss of auto fluorescence (C). The second biopsy showed leukoplakia with mild dysplasia (D). (HE, original magnificaiton × 40).

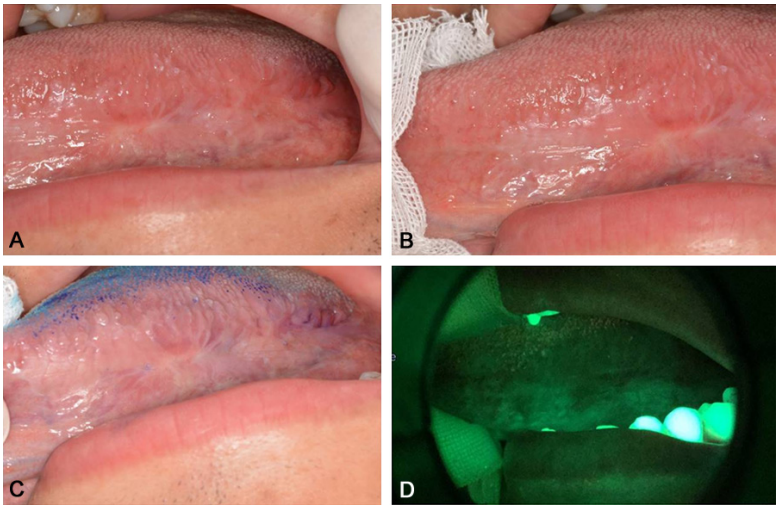

Figure 3. After 16 months of follow up, there were no recurrence or range extention both in operated areas (A) and anterior grey region of abnormal keratosis (B). The TBlue staining was negative (C), and the areas of fluorescence loss have not increased compared before (D).

excision involved the mucosal and submucosal layers. After surgery, the 680 nm low level laser therapy (LLLT) was used in both the operated area and the anterior abnormal keratosis region (continuous output mode, power 100 mW, distance 5-8 mm, 30 S/cm^2, once daily for 2 consecutive weeks). The patient recovered well (**Figure 1**), and the biopsy showed verrucous hyperplasia with mild to moderate dysplasia (**Figure 2**). He was advised to periodic examination every 2-3 months. The monitoring methods included routine oral examination, toluidine blue (TBlue) and autofluorescence detection (VELscope, LED Dental Inc., White Rock BC, Canada). The patient was reexamined for the first time after 5 months of the operation. There were some white plaque areas in front of the operated area with positive TBlue staining, accompanied

by deletion of auto fluorescence (**Figure 2**). Further treatment suggestion was made that to remove the combined positive areas, while the remaining areas of abnormal keratinization were still observed regularly. With his permission, the patient came to our department in February 2016 for the second operation. Under the guidance of TBlue staining, the positive region was excised by high energy diode laser. Low energy laser irradiation on both the operation lesion and abnormal keratoses regions was performed as before. Biopsy findings suggested leukoplakia associated with mild dysplasia (**Figure 2**). The patient recovered well without any obvious discomfort. He has been advised to periodic examinations (every 2-3 months) and accepted LLLT (once daily for 2 consecutive weeks in every 2-3 months). The case was so far followed up for 16 months without any obvious recurrence or enlargement (**Figure 3**).

Discussion

Previous reports of PVL are mostly middle-aged and elderly that progress for 20-25 years [2]. In contrast to those slow-growing PVL, the patient is young and the clinical manifestations were characterized by rapidly multifocal trends and inconsistency of developmental stages. There are areas of gray keratoses, white keratoses and white verrucous proliferation in the adjacent areas at the same time. From hyperkeratosis to verrucous hyperplasia, this to some extent reflects the multiple steps of PVL of the process of development. Clinical manifestations of early PVL may be nonspecific, as we have seen in this case. Lesions may only show some keratinization abnormalities, and the patient has no symptoms. This explains the reasons of most PVL findings are late. There are also references to patients with multifocal oral lichen planus (OLP) presenting as early stage and gradually developing PVL [3]. Although guideline or protocols of diagnostic criteria have been published to provide diagnosis of PVL [4, 5], these criteria are useful only for those reported about long time series, but can be confusing for beginners. We propose the following two clinical criteria to define the early type of PVL: Abnormal keratoses and mutifocal trend. Unlike conventional keratoses abnormalities, PVL patients tend to exhibit multifocal trends rather than confined to one place. This suggests the importance of regular follow-up visits for this type of lesion in the clinical setting. Once the nonspecific abnormal keratoses trends to spread in the follow up, the possibility of early PVL should be considered and monitoring measurements should be taken promptly. Besides visual examination, a variety of new chair-side diagnostic tools are currently available that may enhance early examination [6, 7]. In the follow up, we try to combine TBlue with autofluorescence to detect early lesion. The combined positive region of the two measurements was used as an indication of operation. It is expected to improve the accuracy of monitoring as much as possible through the combination of two different detection methods, reduce the frequency of biopsies, and thus less unnecessary pain. Until now, although TBlue is negative in the follow up, we can still see the absence of fluorescence. We do not operate in these areas because in many previous studies it does not distinguish dysplasia from mucosal inflammation although it can help to find hidden lesions [8, 9]. However, we can see at least that the area of fluorescence deletion has not increased in the careful follow up.

The etiology of PVL is still unknown. Although several authors have suggested that human papilloma virus (HPV), Epstein-Barr virus (EBV) and DNA ploidy abnormality might have a role in the pathogenesis of PVL [10-12], none of these studies have yet be confirmed. The role of tobacco in PVL lesion is also unknown since these lesions are usually seen in nonsomkers [13]. Given these uncertainty, clinicians need to make specific analysis of specific issues for each patient. In this case of young patient, we believe that both external stimuli and internal elements are contributing factors. Prolonged heavy smoking is still one of the major risk factor. Secondly, patients need long-term night work because of occupational reasons, which may lead to the decline of immune function that may also play a role in the development of PVL. The previous report of a patient suffered PVL after bone-marrow transplantation (BMT) also supports this immunity impression [14]. Moreover, PVL patients infected HPV or EB virus might be immunocompromsied like human immunodeficiency virus infected patients [15]. This suggests the possibility of immune-interventions in the early phase of PVL since many patients have shown resistance to therapy in late stages.

Current PVL treatment methods include surgery excision, radiation, photodynamic therapy, systemic chemotherapy [2]. Among these managements, surgery ablation was the most used. Compared with conventional surgery, laser has many advantages such as reduced scar formation, less pain and bleeding, and reduced chances of infection. In this case, we use high-energy laser to remove the verrucous lesion, and we also cooperate with LLLT to both the post-operative lesions and the rest abnormal keratoses areas. As a non-traumatic therapy, LLLT has been found to be efficient in acceleration of wound healing by production of singlet oxygen which in turn promotes RNA and DNA synthesis [16, 17]. On the other hand, LLLT may also trigger the immunological chain reaction which stimulates mast cell and macrophages and also an increased procollagen synthesis [16, 17]. Therefore, besides the post-operative lesion, we also try to apply LLLT to the areas of early abnormal keratoses, and we hope to inhibit the development of early PVL by activating local immunocompetent cells. We confirm that this is the first report of applying LLLT in PVL therapy. Although it will take long time to test how it will turn out, the result is good so far.

Conclusion

Not all PVL progressed slowly, we need to be vigilant about that and take timely steps. The immune status of these patients suggests further examination for its contribution in PVL etiology. In therapy research, how to find effective early intervention could be the most important challenging since PVL in late stage seems to be insensitive to many treatment attempts.

Disclosure of conflict of interest

None.

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