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Pathogenesis, Risk Factors and TCM Treatment of Oral lichen Planus–a Updated Review

IP, Yanting [1*] CAI, Xiaoying [1] ZHANG, Leeyi [1] LIN, Huilin [1] ZHOU, Minhui [1]

[1] Jinan University, China

**** IP, Yanting is the corresponding author, E-mail: xtye1996@163.com***

Abstract: Oral lichen planus (OLP) was first publicly described by Wilson in 1869 as a skin disorder of the oral mucosa that presents with white streaks, white papules, white patches, erythema, vesicles or blisters. It mainly affects the buccal mucosa, tongue and gums. The pathogenesis of OLP is considered as an autoimmune system disease mediated by T cells in which Langerhans cells (LC) function as antigen-presenting cells. Some recent studies suggest that CD4+ cell subsets play a prominent role in the pathogenesis of OLP, and in particular, the dynamic balance between Th1 and Th2 cell subsets is closely related to the pathogenesis of OLP. In addition, it has been proposed that regulation of carcinoembryonic antigen-related cellular adhesion molecule 1 (CEACAM1) by Osteopontion leads to overexpression of CEACAM1, which ultimately activates T cells and promotes basal Perspectives on keratinocyte apoptosis. There are three possible factors associated with the development of OLP. First, it is thought to be related to abnormalities in the body's immune function. Secondly, it is thought to be due to microcirculation disorders in the oral mucosa; thirdly, it is thought that the onset and regression are closely related to the patient's lifestyle habits, negative emotional factors such as anxiety and depressive emotional responses. As the pathogenesis of OLP is still unknown, there is no particularly effective clinical treatment. However, with a large number of comparative clinical efficacy studies, people have discovered the great potential of TCM therapy in the treatment of OLP.TCM therapy has the effect of good efficacy and short treatment cycle, and has gained remarkable clinical efficacy through the use of traditional Chinese medicines to regulate the patient's overall physical state and mental state.

Keywords: Oral lichen planus; Pathogenesis; Risk factor; TCM.

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1 Introduction

Oral lichen planus (OLP) was first publicly described by Wilson in 1869 as a skin disorder of the oral mucosa that presents with white streaks, white papules, white patches, erythema, vesicles or blisters. It mainly affects the buccal mucosa, tongue and gums. The prevalence is 0.1% to 4.0%, and a previous meta-analysis indicated that the prevalence of OLP is about 1.27%, which is the second highest among oral mucosal diseases(Carrozzo). The disease manifests of OLP are small, purplish-red, polygonal flat papules with a glossy surface and white reticulated stripes (Wickham's lines). The rash is mostly distributed on the flexure of the wrists and forearms, the backs of the hands, the forearms, the neck, and the sacrococcygeal region, and can form a linear distribution of new eruptions at the site of scratching (isomorphic reaction). The patient is self-conscious of itching, and the rash may subside after several months to years, with some residual hyperpigmentation. Lichen planus may involve the mucous membranes, most often in the oral cavity, manifesting as a white reticular pattern on the buccal mucous membranes, or vesicles, ulcers, and blisters, accompanied by a burning sensation. Nail lichen planus may occur in some patients, manifesting as thickening, roughness, and unevenness of the nail plate, or atrophy, characteristically manifested as nail pterygium - disappearance of the nail plate, and small skin of the nail covering the nail bed in the forward direction. Oral mucosal lesions are often bilateral and symmetrical , most common in the buccal mucosa , especially in the posterior part of the mucosa ; followed by the tongue , mainly the lateral edge of the tongue ; also occurs in the lips and gums , the palate is less frequently involved. The clinical manifestations of the disease are varied and can be white or red, accompanied by different changes in the texture of the mucosa, which can be broadly divided into reticular and erosive types. Reticular type is the most common, showing interlaced white reticulation, mostly seen in bilateral mucosa; reticulation is not obvious when the formation of white plaques, difficult to distinguish from white spots, commonly found on the back of the tongue. Several immunological studies have been carried out in the past to investigate the pathogenesis, risk factors, carcinogenesis, and clinical therapeutic measures of OLP. In this article, we will present the recent research progress and summaries the pathogenesis, risk factors and carcinogenesis of OLP.

2 Pathophysiology

Its pathogenesis is still unclear. Some early scholars believed that the pathogenesis of OLP may be an autoimmune disease mediated by T cells that function as antigen-presenting cells, Langerhans cells (LC). The possible mechanism is that LC recognizes antigens and activates T cells. Activated T cells release a variety of lymphokines, inducing the dysregulation of HLA-DR antigen expression in keratinocytes, fibroblasts and melanocytes located in the epidermis, ultimately causing T cells to attack the above cells, leading to epithelial damage. The probable mechanism is that LCs recognize antigens and activate T cells. Activated T cells release a variety of lymphokines, which induce dysregulation of HLA-DR antigen expression in keratinocytes, fibroblasts, and melanocytes located in the epidermis, ultimately leading to T-cell attack on these cells, resulting in epithelial damage leading to(D and N). Some immunological studies have also indicated that patients with OLP have a significant decrease in $CD4^+$ cells in the lesion area, a significant increase in $CD8^+$, and a decrease in the $CD4^+/CD8^+$ ratio, which is statistically different from that of the control group, suggesting that the patients' low cellular immunity and the imbalance in the ratio of $CD4^+$ to $CD8^+$ cells are the probable etiological factors of OLP(Wang et al.). The pathogenesis of OLP may include both antigen-specific and non-specific mechanisms(Louisy et al.). The antigen-specific mechanism involves both antigen presentation by basal keratinocytes and destruction of antigen-specific keratinocytes by $CD8^+$ cells. Under certain circumstances, the surface antigens of the basal keratinocytes of the oral mucosa of susceptible individuals may be altered after stimulation with one or more exogenous antigens. LCs located on the mucosal surface take up this antigen and present it to $CD4^+$ cells as an antigenic peptide-MHC II complex, causing them to produce Th1 cytokines. This cytokine has the ability to promote the release of more antigen from the stimulated basal keratinocytes, which ultimately stimulates and attracts the movement of T-cells at the site of the lesion and promotes leukocyte and keratinocyte responses. Aggregated cytokines, chemokines and substances such as CAM activate $CD8^+$ cells to exert a killing effect on keratinocytes or promote their demobilization, leading to OLP. Non-specific mechanisms include mast cell degranulation and matrix metalloproteinase activation. TNF-α released by mast cells promotes T lymphocyte homing, and trypsin and histamine released can damage the epithelial basement membrane directly or indirectly through activation of MMP-9. Subsequent studies have suggested that $CD4^+$ cell subsets play a prominent role in the pathogenesis of OLP, and in particular, the dynamic balance between Th1 and Th2 cell subsets is closely related to the pathogenesis of OLP.

3 Potential for Malignancy

The first case of a patient with OLP developing oral squamous cell carcinoma was reported by Hallopeau et al. in 1910, and the question of whether OLP is precancerous has been controversial. In 1999, ZuoLiang C et al. demonstrated that sun exposure is related to lip cancer, combined with local irritants, hypothesized that cigarette smoking is related to lip OLP carcinogenesis. It was found that the chromosome stability of OLP patients was poor, the aberration rate was high, and they were prone to cancerous changes, which led to the conclusion that "OLP has a weak cancerous potential, and it is only under the influence of external cancer-promoting factors that it undergoes a qualitative change". Many studies show that OLP has potential for malignancy. and that the combination of OLP's own development and systemic factors will lead to malignant changes, so timely treatment is necessary. The study also showed that trauma and psychological stress are associated with OLP based on statistical results. Atena Shiva found that the mean percentage of p53-positive cells was significantly higher in chylous OLP than in non-chylous OLP and normal mucosa, and suggested that high p53 expression could be used to identify OLP lesions with a tendency to become cancerous (Ma et al.).

4 Risk Factors of OLP

Regarding the risk factors of OLP, it is widely believed in the academic community that the disease is closely related to the patient's psychological state, especially negative emotions such as tension and anxiety but still controversial(Allen et al.). RenGang Wu et al.'s study in 1996 pointed out that there may be three factors associated with the development of OLP, firstly, it is thought to be related to abnormalities in the body's immune function. Secondly, it is thought to be due to oral mucosal microcirculation disorders; thirdly, it is thought that the onset and regression of the disease is closely related to the patient's stimulation by strong negative life events and accompanied by anxiety and depressive emotional responses (Wu et al.). Several studies agree with the above views (Wang; Guan and Li; Shi and Zheng). GuoYao Tang et al. found that there may be a relationship between chronic gastritis and the development of OLP by analyzing the clinical outcomes of 126 patients with OLP (Tang et al.). Lihong Zhu study was added for this purpose. Their results showed that in addition to mental status, gender and age are also important factors in the development of OLP, especially middle-aged and older women are susceptible (Zhu et al.). Since then, several population-based studies have found that consumption of irritating foods (chilli, ginger, etc.) is also a significant risk factor for OLP (Qi et al.; Zhu et al.; Xiao et al.; He). In addition to the above factors, Zhou Chun 's team showed that smoking and alcohol habits also increase the risk of OLP (Zhou et al.). Subsequently, Qian Wang 's team from Peking University found that thyroid disease, diabetes mellitus, and hypertension were also risk factors for OLP

through a study of 490 OLP patients from 2010 to 2017. In addition to lifestyle habits, biological factors and systemic diseases are also closely related to the development of OLP. Several studies have found a significant correlation between OLP and Helicobacter pylori infection and hepatitis C virus infection (Zhang et al.; Ji et al.; Yu et al.), revealing that systemic infections may be one of the risk factors for the development of OLP. In addition to this, it has been suggested that mercury metal poisoning is also a risk factor for the development of OLP (Zhou et al.). The possible mechanism is that sub-toxic concentrations of HgCl2 can directly induce the expression of ICAM-1, increase the adhesion of T cells and normal keratinocytes, and also directly stimulate the production of TNF-α, which leads to the aggregation of T cells to the local area and the emergence of immune dysfunction, thus increasing the risk of the development of OLP.

5 TCM Application in OLP treatment

Traditional Chinese Medicine (TCM) treatment is a unique Chinese therapy that judges the basic condition of the human body and treats it with the unique theories and philosophical thinking of TCM. In the theory of Chinese medicine, human being is an inseparable whole and all diseases are caused by the lack of suitable balance between the components of the whole, which are the five most important organs: “Xin”, “Gan”, “Pi”, “Fei” and “Shen”, each of which has its own function and control over different areas of the body. OLP is known in Chinese medicine theory as belonging to the category of "oral chancre", "oral rupture", "purpura" and so on. (Si) According to Chinese medicine theory, this disease is caused by excessive energy stored in the “Xin”, “Gan” and “Wei”, resulting in a state of "Re", coupled with a blockage of the flow of energy in the liver. There are also cases where the body's ability to carry energy is insufficient and the spleen's environment is too "Shi", resulting in weakened function, which ultimately leads to obstruction of the body's circulation, which in the long term can lead to poor circulation and localized inflammation, especially in the epidermis. Multiple clinical efficacy studies in recent years have identified the tremendous application and efficacy potential of TCM in the treatment of OLP. Meta-analyses have shown that TCM combined with conventional medication can significantly improve patients' subjective feelings, reduce their pain, accelerate healing of lesions and shorten the duration of treatment.(You et al.). However, in most cases, TCM does not use the same medicine to treat even in the same disease. Based on the theory of "evidence-based treatment" in Chinese medicine, each case is independent and unique, and the same person living in different places at different times, with different routines and habits may change the overall balance, so the treatment plan used is not the same. This raises the demand for the number of TCM practitioners in clinical treatment, but it should also be taken into account that due to the integrity and complexity of the TCM system, often the number of good TCM practitioners is scarce. There are also studies that are trying to find the comparative efficacy of different TCM therapies in the treatment of OLP in the hope that a stable and effective TCM treatment protocol can be identified. Obviously, the research concept is contrary to the basic theory of TCM, but it is also a good attempt to show that there may be some component of Chinese herbs that can be more effective in treating OLP, and these related studies appear to be heading in that direction, although it is not clear what the results will be. All in all, the therapies and ideas of TCM provide new ideas for the clinical diagnosis and treatment of OLP nowadays, and the maturity of the modern preparation process of TCM is also more conducive to expanding the influence of TCM therapies, but how to ensure the efficacy and effectiveness of TCM therapies as well as doing better in standardization will be one of the hotspots of research in related fields afterwards.

6 Conclusion

The progress of research on the immunological aspects of the pathogenesis and carcinogenesis of OLP is exciting, but at the same time we have to recognize the limitations of applying these findings to clinical treatment. Despite the lack of a clear therapeutic rationale, we cannot ignore the positive effects and benefits that other alternative therapies, such as TCM, can bring to the clinical treatment of OLP. In the future, we can study the clinical effects of various therapeutic options for OLP, including glucocorticoid therapy and non-hormonal immunosuppressive therapy, as well as photodynamic therapy, TCM therapy, or a combination of the above therapies, in order to provide a more effective basis for the clinical treatment of OLP, and at the same time continue to strive for more valuable time for the study of the pathogenesis of OLP, in order to find a specific solution for the treatment of OLP as soon as possible. At the same time, we will continue to strive for more valuable time for the research on the pathogenesis of OLP, so as to seek for a special effective solution for the treatment of OLP at an early date.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Author Contributions

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About the Authors

IP, Yanting

Master in Nutrition and Health, Bachelor in Preventive Medicine, International Practitioner of Faculty of Public Health-UK, IUHPE Registered Health Promotion Practitioner.

CAI, Xiaoying

Undergraduate Student of the school of stomatology of Jinan University.

ZHANG, Leeyi

Undergraduate Student of the school of stomatology of Jinan University.

LIN, Huilin

Undergraduate Student of the school of stomatology of Jinan University

ZHOU, Minhui

Undergraduate Student of the school of stomatology of Jinan University

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