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Rise and exacerbation of oral lichen planus in the background of SARS-CoV-2 infection

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ABSTRACT

Oral Lichen Planus (OLP) is a chronic inflammatory disorder whose exact etiology remains unknown. Inflammatory mediators, cytotoxic CD8+ T cells and mast cells have been hypothesized to mediate the pathogenesis of OLP. COVID-19 pandemic caused by SARS-CoV-2 is marked by cytokine storms in the affected patients. Altered T-cell responses marked by exhaustion of T-cell count with hyperaggressive remaining T-cells and presence of cross-reactive antibodies render infected humans as fertile grounds for development of multisystem disorders. In addition, Vitamin D deficiency in COVID-19 patients can further modify the T cell mediated immunity. Increased circulating cytokines and hyperactive CD8+ T cells can alter the oral immune barriers rendering them susceptible to oral disorders. Due to the widespread immune dysregulation, it is possible that patients of COVID-19 may develop OLP in the aftermath or during recovery. The paper explores the pathogenic mechanism behind development OLP as post-COVID condition on account of their target receptor, T-cell responses, cytokine profile, mucosal immune barriers and nutrition deficiency.

Introduction/Background

Oral lichen planus (OLP) is a chronic inflammatory disorder which has a worldwide prevalence rate of 1.01% [1]. It is the oral counterpart of lichen planus (involve skin, nails, hair, scalp, eyes, urinary tract, larynx and nasal mucosa) [2]. Clinically, oral lesions have been classified as: reticular, papular, plaque, atrophic, erosive, and bullous [3] and; are characterized by periods of exacerbation and remission and; morbidity associated with the recurring lesions [2].

The exact etiology of the disease is unknown although several theories of pathogenesis are afoot in the literature [4–6]. Immune dysregulation is considered to play a pivotal role in pathogenesis of OLP. Inflammatory mediators such cytokines, matrix metalloproteinases and chemokines cause epithelial-connective tissue interface damage or basement membrane liquefaction. Additionally, recruitment of cytotoxic CD8+ T-cells to the lesional sites is mediated by the chemokines which further induce keratinocyte apoptosis leading to clinical erosive and ulcerative lesions [5,7].

Immune dysregulation and cytokine storms remain the hallmarks of the recent COVID-19 pandemic caused by spread of SARS-CoV-2 [8]. It is suggested to be alike autoimmune diseases in terms of it's pathogenesis, manifestations and immune responses [9]. This led to initial identification of 'immune mediated inflammatory diseases' patients as a high risk group for contraction of SARS-CoV-2, though the same was not found to be true [10]. Nevertheless, the debilitating attack on the immune system by SARS-CoV-2 can render the patients susceptible to various co-infections and superinfections [11]. Since immune dysregulation is common to OLP and COVID-19, this paper attempts to explore the possibility of oral lichen planus as a part of the spectrum of post-COVID conditions.

The Hypothesis/Theory

Altered T-cell responses, cross-reactive antibodies, raised cytokine levels, altered immune permeability barrier and Vitamin D deficiency in patients of COVID-19 may lead to rise of OLP or exacerbation of pre-

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existing OLP.

The present theory is analogous to a five-legged stool wherein the following reasons are akin to the supporting pillars of the stool:

1. Related target receptors: SARS-CoV-2 is a highly pathogenic, zoonotic, enveloped virus which belongs to the β-coronovirus family. The target receptor for SARS-CoV-2 is the Angiotensin converting enzyme2 (ACE2) which facilitates the entry of the virus into the host cell. Since high numbers of these receptors are located in the respiratory system, cardiovascular system, urogenital system, gastrointestinal tract and nervous system, they are principal systems affected in patients of COVID-19 [8,12]. Recent identification of high number of ACE2 receptors on the skin and oral mucosa-particularly the epithelial cells of the tongue- via RNA sequence profiling and single-cell transcriptomes flags these sites for their susceptibility to SARS-CoV-2 [13,14]. The local renin- angiotensin- aldosterone system (RAS) of the skin is involved in epidermal proliferation and wound healing. It has been implicated in dermatological disorders such as psoriasis, epidermolysis bullosa, melanoma and scleroderma [15,16]. Angiotensin converting enzyme has also been implicated in pathogenesis of lichen planus though it's exact mechanism is unknown. A single case-control study in 2005 investigated the role of serum and tissue ACE in patients of lichen planus (LP) prior to the institution of therapy via spectrophotometric method using hippuryl-l-histidyl-l-leucine as a substrate. The authors reported significantly raised activity of serum ACE in cases of LP which decreased following therapy. Tissue ACE activity was also increased as evaluated in the biopsies obtained from the cases, however the finding was not significant. The authors pondered upon the potential role of ACE in the pathogenesis of LP- primary, pathogenic or secondary- while recommending it as a biomarker for assessment of therapy effects [17].
2. T-cell responses: Diverse T-cell responses have been reported in COVID-19 patients with majority of the studies conducted in hospitalized individuals. Primarily, initial peripheral lymphopenia, increased functional activity of the remaining T-cells [18] with possible large scale recruitment of the activated T-cells to the lesional tissue sites [19] (p19) have been reported during the acute phase of COVID-19 infection. T-cell counts gradually recover during the recovery phase [20] with deep immunoprofiling demonstrating raised levels of CD38+ HLA-DR+ CD8+ T cells with increased Ki67 expression during the acute phase [21,22] and; presence of CD57+ HLA-DR+ CD11+ T cells [23] and SARS-Cov-2 specific CD8+ T cells [24] during the recovery phase. The long term effects of dynamic upregulation of T-cell subsets with increased expression of NK cell markers and raised cytotoxicity [22] during the convalescent phase are hitherto unknown though reports of cross-reactivity of both CD4+ and CD8+ T cells in SARS-Cov-2 exist in literature [25,26]. A recent study demonstrated cross-reactivity of SARS-Cov-2 antibodies with 28 human tissues (including gut and barrier proteins, gastrointestinal system cells, thyroid, nervous system, heart, joint, skin, muscle, mitochondria and liver tissues) and highlighted them as potential triggers for auto-immune disorders. Selective epitope mapping revealed similarities between viral proteins and mitochondrial M2 protein, F-actin and TPO protein [27]. Considering the same, the potential targeting of oral mucosal antigens via SARS-specific T cells is not unlikely given the distinct structural location (stratified squamous epithelium) of SARS-Cov-2 entry molecules (ACE2, transmembrane protease serine 2 /TMPRSS2, and furin) in the oral cavity [28]. This theory gains traction when one considers the well-established role of T-lymphocytes in production of OLP lesions and that any factor promoting proliferation or cytotoxicity of T-cells will undoubtedly lead to destruction of oral mucosal membranes. Further credence is lent by the recently identified dysregulated mTOR signalling pathway in both SARS-Cov-2 infection and OLP: associated with dysfunctional T-lymphocytes [29,30].
3. Raised cytokines: Several interleukins (IL) such as IL1, 2, 4, 5, 6, 8, 10, 12, 17, and 18 have been implicated in the causation and progression of oral lichen planus [7]. Genetic polymorphisms of IL-18 [31], TNFα [32–35], IFNγ [36–38], IL-10 [33,35], IL-17[39], IL-1ß [34], IL-12 [40], IL-8[41], IL-4[37] have also been associated with OLP. Histopathologically, they damage the basement membrane and cause widespread tissue destruction leading to the formation of clinically observable lesions.

   Cytokine storms have been a hallmark of SARS-CoV-2 infection with IL-1, IL-6, IL-12, IFN-γ, and TNF-α been identified as proinflammatory cytokines causing tissue damage. IL-2, IL-4, IL-7, IL-10, IL-13, IL-17 have also been reported to be raised amongst the patients of COVID-19. In particular, IL-6 has been associated with poor prognosis and acute respiratory distress syndrome in COVID-19 positive patients [42,43]. A linking molecule between T-cells, interleukins, antibody and viral immunity is TRIM21 (Tripartite motif containing-21): a cytosolic ubiquitin ligase which inhibits both viral replication and induces an anti-viral cellular state [44]. In enveloped viruses, TRIM21 gets activated when non-neutralizing anti-nucleoprotein antibody target viral nucleoprotein antigen which results in stimulation of viral specific cytotoxic T cells [45]. SARS-CoV-2 is a single-stranded RNA-enveloped virus and TRIM21 activation may be responsible for the large scale cytokine production and T-cell hypersignatures. Interestingly, overexpression of TRIM21 has also been identified in the lamina propria of OLP lesions via immunohistochemistry (IHC). These TRIM21 over-expressed CD3+ T cells exhibit enhanced IL-6 secretion [46].

   The raised cytokine profiles, dysfunctional T-cells and TRIM21 activation might render the patients suffering or recovering from COVID-19 susceptible to development of oral lichen planus particularly the co-morbid patients due to pre-existing altered immune barrier in them.
4. Immune permeability barrier: The oral mucosa is guarded by the local immunity which develops and evolves in tandem with the commensal microbiota, their metabolites and the immune cells. Similar immune barriers are present in the GIT, brain and skin; are responsible for homeostatic immune responses [47]. Systemic disorders such as diabetes, hypertension and cardiovascular diseases alter oral immune barriers [48–50]. Increased circulating inflammatory mediators and oxidative stress in these disorders may lead to increased susceptibility to cross-reactions with pathogenic organisms manifesting as oral lesions [50,51]. It takes centerstage in light of recent discovery of cross-immune reactivity between SARS-CoV-2 antibodies and cell junction proteins- occludin, zonulin, beta-catenin [27].

   A recent *meta*-analysis has identified hypertension, diabetes, cardiovascular disease, and respiratory disease as risk factors for mortality in COVID-19 patients [52]. In OLP: diabetes, hypertension, psychological stress, Hepatitis C virus, dyslipidemia have been identified as the risk factors [53]. Herein, one has to consider the role of Th17 helper cells (pro-inflammatory) in the induction of oral innate immune responses and; the raised levels of Th17 cells reported independently in both OLP and COVID-19 patients [47,54,55].
5. Vitamin D receptor: Pre-existing T- cell mediated immunity has been theorised to account for varying responses to COVID-19 infection [56]. Vitamin D supplementation has been found to regulate T-cell mediated immunity by modulating T regulatory subsets (CD4+ CD25+ FOXP3+ CD127lo) in healthy individuals and in patients with autoimmune disorders. Higher Treg/total T cell ratios have been associated with higher Vitamin D levels [57]. A systematic review (2020) identifies Vitamin D deficiency as a risk factor for increased lesions of OLP [58]. Recent genetic polymorphic study on Vitamin D receptor in Chinese Han population have identified rs2239185 and rs7975232 variants of Vitamin D receptor for OLP susceptibility [59].

Similarly, Vitamin D deficiency has also been identified as a risk factor for respiratory distress syndrome of COVID-19. Vitamin D receptor activation to improve lung function, regulating renin-angiotensin system and stimulating healing has been suggested by several authors [60,61].

Evaluation of the hypothesis/idea

The design for evaluating the present hypothesis can include cross-sectional testing of each of the above-mentioned factors within two groups: OLP patients with positive history of COVID-19 and; OLP patients without history of COVID-19. Further subgrouping may be done based on the concurrent morbidities. Apart from the mandatory recording of the demographic details, the methodology can revolve around: deep immunoprofiling or deep spatial immunoprofiling of lesional tissue followed by flow cytometry for identification of T-cell subsets; assessment of molecular expression of mTOR pathway via IHC, Western blot or immunofluorescence [62]; IHC based evaluation of TRIM21 and; assessment of 25(OH)D (Vitamin D) levels. Cytotoxicity of CD8+ T cells can be evaluated indirectly via measurement of IFNγ levels or directly via the recently described multiplex screening assay [63].

A prospective study can also be planned in the patients with positive COVID history which would include assessment of salivary biomarkers for OLP occurrence: peroxidation products, vitamin C, vitamin E, cortisol, immunoglobulins (IgG and IgA) [64].

Due to common mechanisms being employed between the two immune dysregulating conditions, it becomes imperative that certain steps are undertaken on war-footing manner by the various oral health care workers worldwide. The present authors suggest a four- pronged strategy to deal with the OLP cases in the aftermath of COVID-19 infections:

1. Tracking and recording of new OLP cases as part of longitudinal multi-country observational studies.
2. Telephonic follow-up of pre-existing OLP cases and encouraging the patients for self-examination and maintenance of record diary.
3. Frequent follow-up of COVID-19 cases with co-morbidities and encouraging the patients for self-examination and maintenance of record diary.
4. Providing mental health assistance to individuals working in high stress environment or having history of psychological disorders.

Discussion and consequences of the hypothesis

Burgos-Blasco et al (2021) reported a single case report of a 56 year old female with oral lichen planus with past positive history of COVID-19 [65]. Since the patient did not have any relevant medical history and was negative for hepatitis C infection; the authors mulled over the idea of COVID-19 being a trigger for OLP. Routray et al has also predicted an increase in OLP in Indian females over 40 years particularly of lower socioeconomic strata due to the increased psychological stress induced via country wide lockdowns, lose of livelihood, lose of loved ones, etc [66].

A recent meta-analysis of 1786 patients on COVID-19 morbidities revealed the most common co-morbidities to be hypertension, cardiovascular and cerebrovascular diseases and; diabetes [67]. OLP has also been associated with several systemic conditions including hypertension, diabetes, psychosomatic disorders [68]. Various studies have reported high levels of stress, anxiety and depression in the aftermath of the COVID-19 pandemic [69]. While long term effects of these psychological disorders within the general population remains to be seen, it is of note that anger control has been correlated with OLP suppression [70]. Hence, one can include anger assessment in the COVID-19 patients as a part of prospective analysis.

OLP is characterized by recurrent period of exacerbation which is associated with patients' immunological, mental and nutritional well being. Recovery from COVID-19 infections can be prolonged and tiresome in some individuals. The Mayo clinic reports that such 'long haulers' may take from weeks to months to recover completely [71]. Post-COVID-19 complications such as OLP can further hinder the recovery process and account for life-long patient morbidity. Institution of the four pronged strategy will allow for early recognition of OLP and institution of treatment. Recognition of the specific pathogenetic mechanism for development of OLP in COVID-19 individuals will determine the treatment strategy. It can vary from simple institution of vitamin D supplementation to T-cell based immunotherapy. Identification of a cross reactivity mechanism will spur development of antibody drugs and institution of immunogenicity assays [72]. Targeted therapy of molecular signalling pathway can allow for the drug repurposing and specific management of the disorder.

Consent statement/Ethical approval

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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