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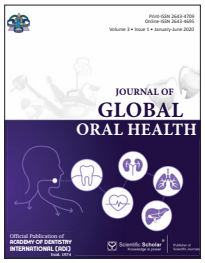

Letter to Editor

COVID-19 and oral cancer, is there a link? A gateway to future research

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Novel corona virus is a global threat worldwide caused by COVID-19 as christened by the World Health Organization (WHO) on February 11, 2020.[1] The international virus classification commission has also named novel coronavirus as SARS-CoV-2 post the outbreak of SARS and MERS. COVID-19 is likely of zoonotic origin based on the large number of infected persons exposed to the wet animal market in Wuhan City, China of COVID-19.[2,3]

The spectrum of clinical manifestations of COVID-19 includes fever, non-productive cough, dyspnea, myalgia, fatigue and normal, or decreased leukocyte counts. They show radiographic evidence of pneumonia, which are similar to the symptoms of SARS-CoV and MERS-CoV infections as we decode the pathogenesis of the novel corona virus.[1,4]

Fang *et al.* reported that causal link between comorbidities such as cerebrovascular diseases, diabetes, coronary heart diseases, and hypertension to the augmented risk of lethal outcome post the viral infection. Patients who are under ACE2-enhancing drugs are at higher risk for a fatal COVID-19 infection.[5]

Patients with cancer or undergoing treatment are in an immuno-compromised state and can easily succumb to COVID-19, with associated worse outcomes. Yu *et al.* assessed the incidence (0.79%) and outcomes of SARS-CoV-2 infection among patients with cancer. The heightened risk was twice the cumulative incidence in Wuhan estimated at 0.37% over the same period. Individuals with cancer who contracted the virus had non-small cell lung cancer; rectal, colon, pancreatic, urothelial, and breast cancer.[6]

Wang *et al.* and Allison *et al.* using epidemiological statistics observed that patients with cancer history were more likely to develop COVID-19 due to the chronic immuno-suppressive state and have a poor prognosis.[7,8]

Oral cancer is considered as the most common cancers, and is a major health problem particularly in developing countries. Among all oral neoplasms, oral squamous cell carcinoma (OSCC) is the most common. Many risk factors have been well established to have significant evidence associated with oral cancer. The etiology of oral cancer is complex and its multifactorial. It is known that tumor microenvironment can modulate the biological behavior of tumor cells.

One such important modulator is the presence of functional renin-angiotensin system (RAS). Angiotensin II (Ang II), a crucial component of RAS has been reported to have protumoral roles in carcinogenesis.

Angiotensin II is produced from the peptide, Angiotensin I (Ang I) by a protease enzyme, angiotensin-converting enzyme (ACE). Angiotensin II exerts its functions by attaching to its receptors Angiotensin II receptor type 1 (AT1R) and Angiotensin II receptor type 2 (AT2R). The ACE is known to be a pivotal enzyme in controlling the RAS. ACE2, a homolog of ACE, is another key enzyme of the RAS, which breaks down Angiotensin II to form Angiotensin 1–7. ACE2 and Angiotensin 1–7 counterbalance the effects of ACE and Angiotensin II, respectively. Angiotensin II is reported to play a key role in carcinogenesis and apart from its systemic actions, it also exerts local effects. It can promote angiogenesis and cellular proliferation. It also mediates the invasion of OSCC cells, thus facilitating its metastasis. Angiotensin II provokes the stromal-tumor paracrine interaction. AT1R mediates the actions of Angiotensin II by receptor phosphorylation and subsequently triggering a chain of intra and extracellular events. ACE, Angiotensin II and AT1R facilitate the pathogenesis of the disease, on the other hand, ACE2, Angiotensin 1–7, and AT2R inhibit the progression of the disease and antagonize the actions of ACE, Angiotensin II, and AT1R. Thus, it is quite evident that ACE2 maintains the balance of RAS as a negative controller.[9]

Substance abuse, smoking and alcohol are established risk factors, however a substantial proportion of young cohorts with no history of substance abuse develop oral carcinoma, emphasizing the role of other risk factors such as genetic susceptibility and oncogenic viruses.

CoVs are positive-stranded RNA viruses with a crown-like appearance under an electron microscope (coronam is the Latin term for crown) due to the presence of spike glycoproteins on the envelope. The subfamily Orthocoronavirinae of the Coronaviridae family (order Nidovirales) classifies into four genera of CoVs: Alphacoronavirus (alphaCoV), Betacoronavirus (betaCoV), Deltacoronavirus (deltaCoV), and Gammacoronavirus (gammaCoV). Furthermore, the betaCoV genus divides into five sub-genera or lineages.[10,11] The transformation from animal host to the human host is yet to be understood also some of its clinical manifestation that mimic common flu to lethal ARDS has perplexed the clinicians as to how to tame the virus.

Recent studies on Covid-19 have indicated that the path of entry of 2019-nCov into a host cell is through the ACE2 cell receptor. The virus attaches itself to this receptor through the S-spike present on the virus surface. ACE2 has been identified as the coreceptor for the corona virus. Intriguingly, ACE2 receptor of this virus is highly expressed on the oral mucosal epithelial cells. The single cell RNA sequence of four samples of oral mucosal tissues was observed and the expression of ACE2 was recorded higher in epithelial cells of tongue than buccal and gingival tissues. The virus expresses a protein, which is known as SPIKE (S protein). This protein contains a receptor binding region, which attaches to the extracellular part of the ACE2. The S protein is broken down into two subunits – S1 and S2 by a host protease TMPRSS2.6. The virus fuses with the membrane and is incorporated through endocytosis with ACE2 into the host cell. Thus, COVID-19 infection causes exhaustion of ACE2 cell receptors. In situations of COVID-19 infection in OSCC patients, there will be reduction in availability of ACE2. This situation will increases the concentration of Angiotensin II, thus could be promoting a protumoral effect mediated by Angiotensin II.[9]

Pathophysiology and virulence mechanisms of CoVs are linked to the function of the nsps and structural proteins which could block the host innate immune response. Among functions of structural proteins, the envelope has a crucial role in virus pathogenicity as it promotes viral assembly and release. However, many of these features (e.g., those of nsp 2, and 11) have not yet been described.[2]

Two-phase immune responses induced by COVID-19 infection

Clinically, the immune response to SARS-CoV-2 infection is two-phase. A specific adaptive immune response is required during incubation and non-severe stages to eliminate the virus and prevent the disease from progressing to serious stages. Hence, rebooting the immune responses (anti-serum or pegylated IFNα) can have a significant role. To develop an endogenous protective immune response during incubation and asymptomatic phase, the host should be in a healthy state and have an appropriate genetic background (e.g., HLA) that generates specific antiviral immunity. Genetic differences are well known to contribute to a person's variations in the immune response to pathogens. However, when a protective immune response is impaired, the virus propagates and massive destruction of the affected tissues occur.[12]

To conclude, further studies are essential to explore and determine the structural characteristics of SARS-COV-2 that underlie the pathogenetic mechanisms. Compared to SARS, for example, initial clinical data show minimal involvement of the respiratory system. Oncogenic virus species have been proposed to be involved in oral carcinogenesis. Although due to the lack of extensive data, it is not possible to draw definitive clinical information. This raises a question toward an association between oral cancer and COVID-19, which opens up a gate for further extensive cohort studies.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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