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THE BIDIRECTIONAL RELATIONSHIP BETWEEN ORAL CANCER AND SARS-COV-2: A PATHOGENIC AND PHARMACOLOGICAL REVIEW

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ABSTRACT
The chances of influenza-related hospitalization or mortality are significantly higher in oral cancer survivors than in people with no cancer. ACE2 is the binding receptor for SARS-CoV-2 which is activated by furin. Host cell surface priming is done primarily by type II transmembrane serine protease TMPRSS2 and to some extent by endosomal cysteine proteases Cathepsin B (Cat B) and Cat L. Stratum granulosum of oral epithelium expresses both ACE2 and TMPRSS2 indicating that SARS-CoV-2 can infect human oral keratinized stratified squamous epithelium by micro laceration. ACE2 overexpression plays a significant role in the progression of oral cancer. Furin promotes epithelial-mesenchymal interaction (EMT) leading to more aggressive neoplasia. Cathepsin B and L are potent biomarkers for oral cancer prognosis. CD147 has been identified as another attachment site for the SARS-CoV-2 virus and is also implicated in tumor cell invasion. Immunosuppression is bidirectionally correlated with COVID-19 infectivity and predisposition to malignancy. Interventional management for oral cancer patients should be done reinforcing standard biosecurity measures. Cross-reactivity of these drugs with anti-COVID agents should be considered when treating OSCC patients coinfected with SARS-CoV-2.

KEYWORDS: Oral cancer, SARS-CoV-2, ACE2, TMPRSS2, Furin, oral cancer chemotherapy.

INTRODUCTION

On 30 January 2020, the World Health Organization (WHO) Director-General raised the WHO's highest level of alarm for COVID 19 and proclaimed the SARS CoV 2 outbreak as a public health emergency of international concern (PHEIC).[1] Since then 207,535,317 people worldwide have been infected with COVID 19 and 4,367,259 have lost their lives to it. The United States of America has witnessed the maximum number of cases reported as 37,435,835 with India slightly trailing behind at 32,192,576 total cases as of August 15th, 2021.[2] Variants of SARS-CoV-2 characterized based on their sequence of amino acid combinations, identified till date are: Variants of Concern (VOC)- Alpha, Beta, Gamma, and Delta. Variants of Interest (VOI)- Eta, Iota, Kappa, and Lambda.[3]

Oral cancer accounts for 4.1% of the incidence rate and 1.9% of the mortality rate of all cancers worldwide. According to the Global Cancer Observatory, 377,713 new cases and 177,757 deaths related to lip and oral cavity cancer were reported in 2020.[4] Oral or mouth cancer is the second most common cancer after lung cancer in Indian men especially in the west and central regions of the Indian subcontinent.[5] The most common cancer variant in the head and neck region is squamous cell carcinoma (SCC). Early detection and management of SCC play a pivotal role in reducing morbidity and mortality.[6]

A metanalytical study spanning Asia, Europe, and the United States including 1,776 cancer patients concurrently infected with COVID-19, reported a significantly higher all-cause mortality in patients with cancer than those without.[7] The chances of influenza-related hospitalization or mortality were reported to be 2.7 times more in cancer survivors (including oral cancer) than in people with no cancer.[8]

SARS-CoV-2 tropism for oral mucosa

The SARS-CoV-2 virus is a positive-sense single-stranded RNA virus with icosahedral morphology.[9] Coronaviruses have four main types of structural proteins at the 3' end of the viral genome namely, spike (S), membrane (M), envelope E, and nucleocapsid (N), and the fifth type hemagglutinin-esterase (HE) which is present in the β-subset.[10] It enters the target cell by fusing its surface glycoproteins termed as spike protein (S) with the ubiquitously present spike-shaped ACE2 binding proteins. ACE2 is expressed abundantly in the lungs and salivary glands. Consequent to the inability to regulate the renin-angiotensin system triggers an inflammatory response. In severe cases, copious

secretion of inflammatory cytokines induces a cytokine storm leading to multisystem impairment.[9]

The spike proteins belong to the category of class I fusion glycoprotein. These highly glycosylated homotrimeric S protein molecules have two distinct functional units, S1 and S2.[11] S2 subunit is the smaller segment and forms the stalk of the spike protein molecule.[10] Virus tropism is elicited by the receptor-binding domain (RBD) of the S1 subunit. This step is mediated by heptad repeat segments and fusion peptides of the S2 subunit. The virus is activated by proteolytic cleavage of the viral S proteins. These S proteins acquire a polybasic cleavage site (PRRAR) at the S1-S2 junction via prototype proprotein convertase furin and another cleavage at the S2 site. Following division at the S2 segment, the virus undergoes profound conformational modifications exposing the RBD unit facilitating viral entry.[11] Thus, ACE2 is the binding receptor, and this receptor binding is activated by furin.[12] Host cell surface needs to be primed for this step which is done primarily by type II transmembrane serine protease TMPRSS2 and to some extent by endosomal cysteine proteases Cathepsin B (Cat B) and Cat L.[11] After fusing with the host ACE2 receptor via endocytosis, the cleaved virus gets incorporated into the host cells.[13]

ACE2 is a type I integral membrane glycoprotein. This carboxypeptidase acts as the key enzyme in the circulatory cascade renin-angiotensin system (RAS) that regulates blood pressure and serum electrolytes.[14] Saliva has a high viral load which correlates with oral manifestations.[9] Increased levels of ACE2 are observed in the lungs of COPD and smokers.[15] On the one hand, smokers are highly susceptible to developing oral squamous cell carcinoma (OSCC), and on the other hand, smoking is believed to enhance ACE2 expression. Nevertheless, whether this can counteract the detrimental effects of tobacco in the COVID scenario is yet to be explored.[13] ACE2 degrades angiotensin (Ang II) and facilitates its binding with type 1 receptor (AGTR1) which in turn expedites proliferation and invasion of OSCC cells. Parallelly, AGTR2 binds with its type 2 receptor releasing anti-apoptotic and anti-oxidative stress phenotypes.[16] ACE influences the proliferation and migration of tumoral cells, angiogenesis, and promotes distant metastasis.[14] ACE2 overexpression plays a significant role in the progression of OSCC. A single cell RNA-sequence-based study validated the potential high risk of the oral cavity for susceptibility to COVID 19 infection. Among the oral tissues, epithelial cells of the tongue demonstrated elevated ACE2 expression as compared to the buccal mucosa or gingiva. ACE2 reactivity was also observed in the lymphocytes within the oral mucous membrane.[17] COVID 19 infection especially in OSCC patients exhausts the ACE2 receptors, which enhances Ang II concentration and its pro-tumoral effects.[13] The invasive attribute of Ang II is mediated in an autocrine and tumor paracrine manner by angiotensin receptor 1 (AT1R) and inhibited by angiotensin 1-7 (Ang1-7).[18] An integrative bioinformatic study reported high ACE2 expression in head and neck squamous cell carcinoma (HNSCC) and a significant role in tumor immune response suggesting a role of ACE2 in the occurrence and development of HNSCC.[19]

Furin is a widespread calcium-dependent protease expressed as a 794 amino acid zymogen. Hypoxia induces intracellular localization of furin. Furin overexpression and protease inhibition are implicated in tumorigenicity and invasiveness of head and neck cancers. [20] Immunohistochemistry (IHC) based study evaluated the reactivity of furin and vascular endothelial growth factor C (VEGF-C) along with microvessel density (MVD) in glossectomy samples. The most aggressive tongue SCC samples exhibited the highest furin level which in turn was responsible for VEGF-C processing. A resultant increase in angiogenesis with increased MVD indicated enhanced invasiveness.[21] Furin is also reported to promote epithelial-mesenchymal interaction (EMT) via the Hippo-YAP pathway thus leading to more aggressive neoplasia.[22]

Stratum granulosum of oral epithelium expresses both ACE2 and TMPRSS2 indicating that SARS-CoV-2 can infect human oral keratinized stratified squamous epithelium by micro laceration. [23] Neoplastic tissues from the head and neck and lungs exhibit reduced expression of TMPRSS2 conferring resistance to SARS-Cov-2 infection. This reduction was more evident in HNSCC patients who are HPV negative and mutated for the TP53 gene with poor overall and disease-free survival.[24] In contrast, a previous IHC based study reported high expression of TMPRSS2 in head and neck cancer patients which correlated with the severity of cancer-related pain modulated via the PAR-2 dependent mechanism.[25]

Cathepsin B is present at high levels in the oral tissues especially the gingival crevicular fluid and the submandibular gland. It contributes to uncontrollable proteolysis and its overexpression is reported to positively correlate with a higher grade of OSCC and lymph node metastasis.[26,27] Cathepsin L functions as a cleavage molecule and is a potent biomarker for cancer prognosis.[26]

Recently, EMMPRIN or BASIGIN / CD147 has been identified as another attachment site for the SARS-CoV-2 virus. This cell surface glycoprotein is a member of the immunoglobin superfamily and is significant in the growth and differentiation of a variety of tissues. EMMPRIN activates certain matrix metalloproteinases such as MMP-1, MMP-3, and MMP-9, which are implicated in tumor cell invasion. It also upregulates the reactivity of monocarboxylate transporters-1 (MCT-1) and MCT-4 that supervise metabolic reprogramming of tumor cells.[28] An IHC based study reported a correlation between overexpression of CD147 and

hypoxia-inducible factor 1a (HIF-1a), VEGF-A, and VEGF-C levels. This association resulted in recurrence and worse overall survival in tongue OSCC patients.[29] The role of different biological molecules in COVID and OSCC is summarized in Table 1.

Immunopathogenic relation between COVID-19 and Oral Cancer

SARS-CoV-2 infection elicits host immune response activating both innate and adaptive immunity. CD8 + T cells attack the virus-infected cells directly while CD4 + T cells activate the B-cells to synthesize immunoglobulins such as IgG and IgM. T helper cells assist in the attack by releasing pro-inflammatory cytokines. The complement pathway produces C3a and C5a to fight the infection. To combat the host immune strike the SAR-CoV-2 virus induces apoptosis of the T cells. In hosts with impaired or abnormal or exaggerated immune response, a prolific upsurge of inflammatory mediators associated with a cytokine storm coupled with free radicals and profound tumor-based lymphopenia, are deleterious to the host organs.[30]

The concept of tumor-infiltrating lymphocytes (TILs) highlights the role of immunological basis in cancers.[31] Immunosuppression is bidirectionally correlated with advanced age and predisposition to malignancy. Incidence of malignancy increases 100 folds with primary immunodeficiencies. Head and neck cancers are associated with decreased cell-mediated immunity with diminished immune reactivity as cancer progresses.[32] Antigen-presenting cells (APCs) present the antigen proteins to the T cells thus activating them. In turn, these effector T cells induce an anti-tumor cascade. Nevertheless, tumor cells escape immune surveillance by developing resistance.[31]

The immune system has a dual role in carcinogenesis. On the one hand, it inhibits tumor cell proliferation while on the other hand, it either selects tumor cells that are potentially fit enough to survive in an immune-compromised host or induces a conducive environment for their growth. Immunotolerance is the primary mechanism associated with cancer development. Immunosenescence or age-associated impairment of immune surveillance is the pathogenic mechanism involved in the increased susceptibility of immunocompromised elderly to induction of carcinogenesis.[33]

Role of Smoking in COVID-19 and Oral Cancer

Active smoking plays a perplexing role in increased predisposition to COVID pneumonia. Cai G et al reported a 25% increase in ACE2 expression in the lungs of smokers with consequently increased facilitation of viral binding sites. Furin expression increased to a lesser extent than ACE2 while TMRPSS2 was independent of smoking status.[34] Yet the prevalence of COVID-19 in active smokers has been reported to be low contradicting the role of smoking in COVID-19 pathogenesis.[35] Various hypotheses have been put forth to clarify this discrepancy. Tobacco might induce structural alterations in the ACE2 allele inhibiting its binding with SARS-CoV-2.[36] Tobacco also causes epigenetic changes in the oral mucosa by immunosuppression and release of toxic substances that induce oxidative stress, thus stimulating oral carcinogenesis.[37]

Management of Oral Cancer patients infected with COVID-19

Based on the ESMO guidelines, oral cancer patients with cT2-cT4 fall under the category of high priority while cT1 is high/ medium priority among the head and neck cancer patients.[38] Unlike management of cancer from other sites in the head and neck region, the main treatment strategy for oral cancers is surgical resection. For advanced-stage disease, multimodal therapy with adjuvant radiotherapy or chemoradiotherapy, or immunotherapy is employed based on the Tumour (T) and node (N) staging following resection of the primary tumor and lymph node dissection. An oncologic COVID-19 infected patient in need of urgent surgical intervention and who is otherwise healthy can undergo surgery in the same way as non-COVID oncologic patients. Care should be taken to reinforce standard biosecurity measures and the patient should be thoroughly monitored throughout the recovery period. Operatory personals in the surgical unit of head and neck cancers are at extremely high risk of being exposed to SARS-CoV-2 aerosolization and transmission. Considering this high risk of spread, it is postulated to reschedule elective surgical procedures except in time-sensitive patients with unavoidable emergencies.[6] Appointments should be prioritized based on patient screening and triage.[39] A risk-benefit analysis should be done on a case-to-case basis and in patients wherein non-surgical management can provide similar results as surgical management without compromising the patient's wellbeing, non-surgical management is recommended.[6] Postoperative review and rehabilitation are imperative in oral cancer management.[40] Follow-up appointments should be suitably longer,[6] and telemonitoring should be considered in feasible situations.[39]

Chemotherapy for Oral Cancer and its interaction with COVID-19 therapeutics

Following surgical resection of the tumor, patients are sometimes required to undergo chemotherapy to eliminate residual tumor cells, while large cancers require induction chemotherapy or neoadjuvant chemotherapy to reduce the size of the tumor to make it amenable for surgery. Cross-reactivity of these drugs with anti-COVID agents should be considered when treating OSCC patients coinfected with SARS-CoV-2.[41,43] (Table 2). The National Comprehensive Cancer Network (NCCN) Chemotherapy Order Templates categorizes conventional chemotherapeutic agents into antimetabolites (Methotrexate, 5-Fluorouracil, Capecitabine), Platinum-based agents (Cisplatin, Carboplatin), and Plant alkaloids (Paclitaxel

Docetaxel).[44] For treating metastatic head and neck cancer, TPEx is the commonly used protocol. It is advised to adopt a Q2W schedule with reduced doses (40 mg/m^2) of cisplatin and docetaxel and 500 mg/m^2 of cetuximab.[41] Most of the anticancer agents such as cisplatin and taxanes cause myelosuppression while cancer radiotherapy produces a mitotic catastrophe which consequently increases the risk for COVID-19 infectivity.[45]

COVID-19 Vaccination and Oral cancer

Goshen-Lago et al examined the seroconversion rate and the safety profile of the BNT162b2 vaccine in cancer patients (head and neck cancer patients accounted for 5% of the study population). Only 29% of the study population responded seropositive after the first dose but with the second dose, the seropositivity rate increased dramatically to 86%. The vaccine appeared to be safe especially for patients with solid tumors undergoing active anticancer therapy.[46] Live vaccines such as Bacillus Calmette–Guérin are contraindicated in patients undergoing immunosuppressive therapy.[47]

Table 1: Bidirectional role of different biological molecules in COVID and OSCC.

Biological molecule	Role in COVID	Role in OSCC
ACE2	Attachment site for the viral Spike protein	Proliferation and migration of tumoral cells, angiogenesis, and promotes distant metastasis
Furin	Activation of receptor binding	Tumorigenicity and enhanced invasiveness of tumour cells
TMPRSS2	Priming of host cell surface	Higher expression correlated with severity of cancer related pain
Cathepsin B and L	Priming of host cell surface	Uncontrollable proteolysis and a potent biomarker for cancer prognosis
EMMPRIN or BASIGIN/ CD147	Alternate attachment site for the SARS-CoV-2 virus	Recurrence and worse overall survival

Table 2: Drug interaction between anti-Cancer agents and anti-COVID agents.

	Lopinavir/ Ritonavir		**Hydroxychloroquine**		**Azithromycin**		**Remdesivir**		**Colchicine**		**Tocilizumab**	
	Serum concentration	Adverse effects	Serum concentration	Adverse effects	Serum concentration	Adverse effects	Serum concentration	Adverse effects	Serum concentration	Adverse effects	Serum concentration	Adverse effects
Methotrexate	Increased level of Methotrexate	Hepatotoxicity	Decreased level of Methotrexate	No interaction expected	Increased level of Methotrexate	Hepatotoxicity	Increased level of Methotrexate	Hepatotoxicity	Increased level of Methotrexate	Myopathy, rhabdomyolysis, and myoglobinuria	Decreased level of Methotrexate	Liver damage
5-Fluorouracil	Increased level of Fluorouracil	Prolongation of QT interval	Increased level of Fluorouracil	Prolongation of QT interval	Increased level of Fluorouracil	Prolongation of QT interval	Increased level of Fluorouracil	No interaction expected	Increased level of Fluorouracil	No data	Decreased level of Fluorouracil	Increased immunosuppressive action
Capecitabine	Increased level of Capecitabine	Prolongation of QT interval	Increased level of Capecitabine	Prolongation of QT interval	No interaction expected	Prolongation of QT interval	No interaction expected	No interaction expected	Increased level of Colchicine	No data	Decreased level of Capecitabine	No data
Cisplatin	Increased level of Cisplatin	Nephrotoxicity	Increased level of Cisplatin	Neuropathy	No interaction expected	No interaction expected	No data	Nephrotoxicity	Increased level of Cisplatin	Uricemia	Increased level of Cisplatin	Increased severity of adverse effects
Carboplatin	Increased level of Carboplatin	No interaction expected	Increased level of Carboplatin	Neuropathy	No interaction expected	No interaction expected	No data	Nephrotoxicity	Increased level of Colchicine	No data	Increased level of Carboplatin	Increased severity of adverse effects
Cetuximab	No interaction expected	No interaction expected	No data	No interaction expected	No data	No interaction expected	No data	No interaction expected	No data	No data	No data	Increased severity of adverse effects
Docetaxel	Increased level of Docetaxel	No interaction expected	Increased level of Docetaxel	Neuropathy	Increased level of Docetaxel	No interaction expected	Increased level of Docetaxel	No interaction expected	Increased level of docetaxel	No data	Decreased level of Docetaxel	No data
Paclitaxel	Increased level of Paclitaxel	No interaction expected	Increased level of Paclitaxel	Neuropathy	Increased level of Paclitaxel	No interaction expected	Increased level of Paclitaxel	No interaction expected	No data	Myopathy, rhabdomyolysis, and myoglobinuria	Decreased level of Paclitaxel	No data

CONCLUSION

Certain biological molecules play a dual role in oral carcinogenesis and SARS-CoV-2 molecular mechanism increasing the propensity of oral cancer patients for SARS-CoV-2 infectivity. COVID-19 being an immune-mediated disease has an increased preference for cancer which is characterized by immunosenescence. Surgical management of oral cancer patients co-infected with COVID-19 should be deferred/postponed if feasible. Interventional decisions should be based on risk-benefit assessment on a case-to-case basis. Chemotherapeutic agents can be used based on international oncological guidelines with keen attention to the drug interactions with COVID-19 therapeutic agents. Vaccines seem safe to administer though these patients tend to display delayed sero-response. Successful management of this epidemic warrants prompt action and a holistic approach to limit its spread. Cancer patients are especially vulnerable to all sorts of infections. Healthcare professionals from all domains should be actively involved to provide supportive care and state of art treatment facilities. Dentists and oral pathologists can play a pivotal role in the early diagnosis of oral cancer and resultant improved quality of life.

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