



COVID-19 and oral cancer: Critical viewpoint

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Abstract

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has marked the beginning of a new pandemic named coronavirus disease 2019 (COVID-19). The World Health Organization has announced it as a health emergency that is of international concern. The disease has been reported to cause respiratory illness, pneumonia and even hinder the immunity of an individual. Individuals with disturbed immune responses have been found to be quite susceptible to this viral infection. Oral cancer patients are also at high risk in this pandemic situation and might encounter severe detrimental outcomes. Angiotensin receptors, documented in studies as the path of entry of this virus, are highly expressed in the epithelial cells of oral mucosa, making the group of individuals with oral cancers even more vulnerable. Extracellular matrix metalloproteinase inducer is another potential target for SARS-CoV-2. An exhaustion of angiotensin converting enzyme 2 cell receptors leads to protumoral effects, whereas a downregulation of extracellular matrix metalloproteinase inducer leads to antitumoral effects. Thus, it causes a variation of the biological behavior of the tumor. This article focusses on the molecular mechanisms, effects and pathophysiology of COVID-19 in oral squamous cell carcinoma patients. The different molecular changes in oral squamous cell carcinoma in the background of COVID-19 will modify various environmental factors for this pathology and have an effect on the carcinogenesis process. Understanding the behavior of the tumor will help plan advanced treatment strategies for oral squamous cell carcinoma patients in the background of COVID-19.

Key Words: COVID-19; SARS-CoV-2; Oral cancer; Head and neck carcinomas; Oral squamous cell carcinoma

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Core Tip: The outbreak of coronavirus disease 2019 (COVID-19) has evoked concern worldwide. The rapid spread of the disease during the first and the second waves caused severe respiratory illness. Individuals are facing a suppressed immune response. An impaired immune response has made patients with head and neck cancer highly susceptible to the viral infection. The two potential receptors of severe acute respiratory syndrome coronavirus 2, angiotensin receptors and extracellular matrix metalloproteinase inducer, have contrasting effects on cancer progression. Thus, the molecular mechanisms and the biological behavior of oral squamous cell carcinoma show varying effects in the background of COVID-19.

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TO THE EDITOR

The outbreak of coronavirus disease 2019 (COVID-19) has posed a major health impact, affecting populations all over the world with significant morbidity and mortality. With the introduction of the second wave in many countries, the doubling time of infectivity has reduced drastically. This also means that we should doubly prepare for all the consequences that we faced in the first wave. Individuals with disturbed immune responses have been found to be quite susceptible to this viral infection. Cancer patients have been considered to be at high risk in this pandemic situation because of immunosuppression[1]. Not only the underlying malignant condition but also co-morbidities, advanced age and poor host response have been held responsible for the vulnerability of cancer patients during the COVID-19 pandemic[2,3].

Studies have identified the angiotensin converting enzyme 2 (ACE2) cell receptors as the path of entry of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) into a host cell[4]. ACE2 receptors are reportedly found to be highly expressed on the epithelial cells of oral mucosa making the group of individuals with oral cancers even more vulnerable. ACE2, a key enzyme of renin-angiotensin system, breaks down angiotensin II (Ang II) into Ang 1-7[5]. Ang II is a protumoral agent that plays a major role in carcinogenesis[6]. It helps in tumor cell proliferation and angiogenesis. It also facilitates the metastasis of cancer cells. Thus, Ang II aids in progression of the disease, while ACE2 and Ang 1-7 inhibit the progression. ACE2 maintains a balance of renin-angiotensin system[5]. However, these propositions might alter due to changes in the viral component, specially mutation in the spike protein.

The SARS-CoV-2 attaches to ACE2 cell receptors through the S-spikes on the virus surface. The SPIKE (S protein) expressed by the virus attaches to the extracellular part of ACE2 receptors, and the S protein breaks down into subunits S1 and S2[7]. The virus fuses with the cell membrane and gains entry into the cell *via* endocytosis. An exhaustion of ACE2 receptors takes place due to the viral infection. ACE2 receptors being highly expressed in tongue, gingiva and buccal epithelial cells, oral squamous cell carcinoma (OSCC) patients are at high risk during this pandemic[7]. The viral infection will cause a reduction in ACE2 concentration leading to an increase in Ang II concentration[5]. This could have a protumoral effect facilitating the progression of OSCC.

Besides ACE2 receptors, extracellular matrix metalloproteinase inducer (EMMPRIN), also known as BASIGIN/CD147 has been identified as another potential target for SARS-CoV-2[8]. EMMPRIN is a cell surface glycoprotein belonging to the immunoglobulin family. It helps in activation of molecules of several matrix metalloproteinases. Thus, it helps in proliferation of tumor cells and their invasion and migration[9]. EMMPRIN also promotes angiogenesis by stimulating vascular endothelial growth factors in the tumor microenvironment[10]. It is speculated that EMMPRIN expression is increased in oral carcinogenesis. The upregulation of EMMPRIN expression in OSCC patients might make them more susceptible to COVID-19 infection[8]. The virus attaches itself to EMMPRIN receptors through S receptors; thus, COVID-19 in OSCC patients will lead to downregulation of EMMPRIN receptors. This will inhibit the progression of the tumor due to scarcity of EMMPRIN receptors.

The COVID-19 infection in OSCC patients will reduce the availability of ACE2 receptors. This will lead to upregulation of Ang II concentration, thus promoting carcinogenesis. In such situations of nonavailability of ACE2 receptors, SARS-CoV-2 attaches to its next potential target, EMMPRIN receptors, to gain entry into the host cells[8]. This in turn causes downregulation of EMMPRIN receptors leading to antitumoral effects. The two potential receptors of SARS-CoV-2 have contrasting effects on OSCC progression.

COVID-19 infections in OSCC patients modulate the events of carcinogenesis and control the biological behavior of the tumor. Future molecular studies are required to have a better insight into the role of the two receptors in the pathophysiology of OSCC. Moreover, angiotensin converting enzyme

inhibitors and angiotensin receptor blockers, which are administered in cancer patients, have been thought to have varying effects on tumor progression. The use of these drugs in OSCC patients during this pandemic still remains doubtful and requires clinical studies.

The expression of ACE2 in various pathologies like oral cancer, oral submucosa fibrosis and periodontitis modulate their disease process. The biological behavior of not only OSCC, but also other oral potentially malignant disorders, in the background of COVID-19 requires in-depth studies and research. This can only be achieved by representative clinical material, *i.e.* COVID-19 positive OSCC patients, appropriate disease model and their long-term follow-up. While keeping these interactions in mind, one should not forget the delay in cancer treatment worldwide. The COVID-19 pandemic has caused deviation of attention from many medical emergencies; cancer and OSCC is not an exception to it. Thus, it is mandatory to formulate guidelines for safe and effective delivery of therapeutics to cancer patient in this difficult time.

Impact of the pandemic on cancer management

Due to mandatory lockdowns during the pandemic, many healthcare specialty services were affected including cancer management. Many countries reported more than 50% reductions in the registration of new cancer patients[11]. These repercussions of the pandemic are mainly related to travel restrictions, conversion of hospitals to COVID-19 centers, fear in the mind of patients, human resource shortages, *etc.* To mitigate the reduction in the number of cases many cancer hospitals have started telecommunication and teleconsultations, but it is premature to comment on its effectiveness especially for head and neck cancer.

Due to compromised primary medical and dental services across the world, the early detection of oral cancer is at stake. Already, head and neck cancers are detected at advanced stages; further delay in the detection would lead to extremely poor prognoses. According to one study in the United States, there was a 25% reduction in newly diagnosed oral cancer cases[12]. Currently, COVID-19 is at declining stages in many countries, and this opportunity should be exploited to perform maximum screening for early detection.

FOOTNOTES

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