JBUON 2021; 26(5): 1719-1722
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

SPECIAL MOLECULAR REVIEW

Impact of SARS-CoV-2 infection on oral carcinoma patients

Vasileios Ragos[1], Maria Adamopoulou[2], Arezina Manoli[3], Spyros Katsinis[3], Sotirios Papouliakos[4], Odysseas Dimas[5], Evangelos Tsiambas[6], Dimitrios Roukas[7], George Papanastasiou[1], Despoina Spyropoulou[8], Loukas Manaios[9], Asimakis Asimakopoulos[10], Nicholaos Mastronikolis[11], Fragiski Anthouli-Anagnostopoulou[12]

[1]Department of Maxillofacial, Medical School, University Hospital of Ioannina, Ioannina, Greece; [2]Molecular Microbiology & Immunology Lab, Department of Biomedical Sciences, School of Health and Care Sciences, University of West Attica, Athens, Greece; [3]Department of Otorhinolaryngology, Thoracic Diseases General Hospital "Sotiria", Athens, Greece; [4]Department of Otolaryngology, GNA Hospital ''Gennimatas'', Athens, Greece; [5]2nd Department of Internal Medicine, ''Gennimatas'' General Hospital, Athens, Greece; [6]Department of Cytology, 417 VA Hospital, Athens, Greece; [7]Department of Psychiatry, 417 VA Hospital, Athens, Greece; [8]Department of Radiology, Medical School, University of Patras, Patras, Greece; [9]Department of Surgery, ''BIOCLINIC'', Athens, Greece; [10]ENT Department, Sion Hospital, Sion, Switzerland; [11]Department of Otolaryngology, Medical School, University of Patras, Patras, Greece; [12]Anatomy & Pathology Lab, Department of Biomedical Sciences, School of Health and Care Sciences, University of West Attica, Athens, Greece

Summary

Coronavirus-related Severe Acute Respiratory Syndrome (SARS-CoV) in 2002/2003, Middle-East Respiratory Syndrome (MERS-Cov) in 2012/2013, and especially the current 2019/2020 Severe Acute Respiratory Syndrome-2 (SARS-CoV-2) tested the national health systems' endurance worldwide. In order to fight this emergency situation, a variety of pharmaceutical companies focused on the design and development of efficient vaccines that are considered necessary for providing a level of normalization in totally affected human social-economical activity worldwide. COVID-19 led to an increased uncertainty in the field of oncological patients' management disrupting the normal conditions of therapeutic and monitoring procedures. In the current article, we explored the impact of SARS-CoV-2 infection on oral carcinoma patients. We observed COVD-19 pandemic negatively affects the normality regarding early diagnosis and optimal management (surgical operation, post-operational follow up/monitoring) in HNSCC/OSCC patients. Understanding the involvement of SARS-CoV-2 in the progression of malignancies is the first critical step for targeting the virus by efficient monoclonal antibodies and vaccines.

Key words: *COVID-19, SARS-CoV-2, oral, carcinoma, vaccines*

Introduction

It is well known now that coronavirus Disease 2019 (COVID-19) is a rapidly globally spread pandemic -characterized by elevated rates of infectivity and mortality- increased the need and pressure for design and development of specific anti-SARS-CoV-2 targeted therapeutic strategies via monoclonal antibodies (mAbs) and also for massive production of safe and effective vaccines [1]. In fact, Coronavirus-related Severe Acute Respiratory Syndrome (SARS-CoV) in 2002/2003, Middle-East Respiratory Syndrome (MERS-CoV) in 2012/2013, and especially the current 2019/2020 Severe Acute Respiratory Syndrome-2 (SARS-CoV-2) affected negatively the national health systems' endurance worldwide. In order to face this emergency situation, many pharmaceutical companies focused on the design and development of efficient vaccines that are considered necessary for providing a level

Corresponding author: Evangelos Tsiambas, MD, MSc, PhD. Cytologist. 17 Patriarchou Grigoriou E´ Street, Ag. Paraskevi, 153 41 Athens, Greece.
Email: tsiambasecyto@yahoo.gr
Received: 31/08/2021; Accepted: 16/09/2021

This work by JBUON is licensed under a Creative Commons Attribution 4.0 International License.

of normalization in totally affected human social-economical activity worldwide [2,3]. Since now, a variety of vaccine types have been under development, validation or even some of them have already completed these stages, approved by Food and Drug Administration (FDA), European Medicines Agency (EMA) and other national health authorities for commercial purposes (*in vivo* use in general population), accelerating their production and distribution process. Among them, novel, innovative nucleoside-modified viral messenger RNA (v mRNA) - based vaccines encapsulated within nanoparticles - specifically lipid ones (LNPs) - are now well recognized [4]. Although this is a very promising aspect of genetic engineering research and application in the field of nano-pharmacogenomics and targeted nucleic vaccines, there is no extended experience and strong data in depth of time regarding their safety, efficacy, and immune response (active immunization levels) that could realistically provide to the general vaccinated population worldwide [5-7].

In the field of oncology, COVID-19 led to an increased uncertainty in the field of oncological patients' management disrupting the normal conditions of therapeutic and monitoring procedures [8-10]. In the current article, we explore the impact of SARS-CoV-2 infection on oral carcinoma patients.

SARS-CoV-2 protein and genomic profile

According to extensive genetic analyses, SARS-Cov-2 virus belongs to lineage b of beta-CoVs demonstrating a strong phylogenetic similarity with BatCoVRaTG13 type [11]. Concerning its genomic structure, a large non-segmented, positive-sense RNA molecule of approximately 30 kb has been detected and analyzed in conjunction with the corresponding RNA-dependent RNA-polymerase (Rd-Rp) that is essential for its replication in the cytoplasm of the target epithelial cells. Analyzing SARS-CoV-2 spherical virion's structure (diam~100nm), research groups have confirmed that there are four main proteins including the spike surface glycoprotein (S), the main or matrix protein (M), the envelope protein (E), and finally the nucleocapsid protein (NC), whereas a variety of non-structural proteins have been also identified. In fact, 16 non-structural proteins (NSP1–NSP16) that encode for the RNA-directed RNA polymerase, helicase, and other components required for virus replication have been reported, whereas the functional role of other seven accessory proteins (ORF3a–ORF8) remains under investigation [12-14]. S glycoprotein projections -consisting of two subunits S1/S2- provide a unique crown-like formation (corona) on virion's surface. Concerning their functional role, S1 represents the main receptor-binding domain (RBD), whereas S2 is involved in the virus-cell membrane fusion mechanism interacting with proteases, such as furin, thrypsin, cathepsin or serino-protease TMPRSS2 [15-17]. Novel molecular and structural/crystallographic analyses have focused on a specific cell membrane receptor - the human angiotensin-converting enzyme 2 (hACE2) - which is the main target-functional receptor for SARS-CoV-2 cell attack, attachment and entry that leads to S1 and S2 subunits activation [18]. Interestingly, h ACE2 mediated SARS-CoV-2 cell entry seems to trigger a variety of intracellular signaling pathways, including hypoxia regulatory molecules [19]. Furthermore, aaccording to the latest published epidemiologic data, SARS-CoV-2-mediated COVID-19 pandemic demonstrates aggressive clinic-pathological profiles in significant subsets of the infected patients –especially in males- and for this reason the role of chromosome X that hosts the hACE2 gene (band Xp22.2) seem to be critical [20].

SARS-CoV-2 infection in oral carcinoma patients

Oral squamous cell carcinoma (OSCC) represents a major malignancy in Head and Neck Squamous Cell Carcinoma (HNSCC) super-family. This pathological entity is frequently characterized by an aggressive phenotype due to an increased tendency to locally and distant lymph nodes metastasize, as a result of severe genetic alterations [21]. Etiopathogenetic factors that lead to OSCC development and progression include tobacco, alcohol chronic consumption and also viral mediated deregulation [22]. Concerning viral oncogenic activity, persistent Human Papilloma Virus (HPV) infection is responsible for malignant transformation of the affected oral/oropharyngeal epithelia modifying the host cell genome [23].

Approaching the efficacy of SARS-CoV-2 related COVID-19 pandemic in OSSC patients, there is increased published experience. Because hospitals in India were hardly affected in initial and also second phase of the pandemic, onco-surgeon teams observed that the management of OSCC was not appropriate for the clinical severity of the corresponding patients. Interestingly, they reported decreased survival rates of newly diagnosed OSCC patients as a result of high incidence of advanced stage disease during the initial phase, n which many patients remained inoperable [24]. The impact of surgical operations delays on these patients and other with a variety of HNSCCs was the topic of another retro-

spective cohort study [25]. The study group of the current research used the optimal time-to-surgery (TTS) as a reliable factor for analyzing the data of a large group OSSC eligible for malignant tumor surgical excision. They concluded that the time limit of 67 days after diagnosis in order these patients to be operated were critical for the biological behavior of the malignancy. A significantly elevated risk for death was observed in patients that had been surgically operated with delay and exceeded this time limit. Additionally, another study group tried to describe and suggest potential new, efficient strategies in order oral malignancies progression to be restrained and stabilized [26]. Similarly, another study focused on the influence of COVID-19 on OSCC patients' morbidity and mortality reported increased rates in them, especially in patients with a history of systematic tobacco and alcohol consumption combined mainly but not always with the toxic side effects that chemotherapy and radiotherapy regimens cause in them [27]. The same progressively aggressive behavior of the malignancy under the influence of SARS-CoV-2 infection pressure was revealed by two studies focused on oropharyngeal SSC and OSSC, respectively [28, 29]. Concerning the molecular mechanisms that are implicated in HNSCC/OSCC patients affecting their clinical features, ACE2 and TMPRSS2 expression in the corresponding malignant tissues demonstrate differences. A study group reported reduced TMPRSS2 expression and imbalances in h ACE2 expression [30-32].

In conclusion, COVID-19 pandemic negatively affects the normality regarding early diagnosis and optimal management (surgical operation, post-operational follow up/monitoring) in HNSCC/OSCC patients. Understanding the involvement of SARS-CoV-2 in the progression of malignancies is the first critical step for targeting the virus by efficient monoclonal antibodies and vaccines.

Conflict of interests

The authors declare no conflict of interests.

References

1. Barh D, Tiwari S, Weener ME et al. Multi-omics-based identification of SARS-CoV-2 infection biology and candidate drugs against COVID-19. Comput Biol Med 2020;126:104051-57.
2. Song Z, Xu Y, Bao L et al. From SARS to MERS, thrusting coronaviruses into the spotlight. Viruses 2019;11:E59-63.
3. Flanagan KL, Best E, Crawford NW et al. Progress and Pitfalls in the Quest for Effective SARS-CoV-2 (COVID-19) Vaccines. Front Immunol 2020;11:579250-58.
4. Dai L, Gao GF. Viral targets for vaccines against COVID-19. Nat Rev Immunol 2020;1-10.
5. Chung YH, Beiss V, Fiering SN, Steinmetz NF. COVID-19 Vaccine Frontrunners and Their Nanotechnology Design. ACS Nano 2020;14:12522-37.
6. Fuller DH, Berglund P. Amplifying RNA vaccine development. N Engl J Med 2020;382:2469-71.
7. Lee WS, Wheatley AK, Kent SJ, DeKosky BJ. Antibody-Dependent Enhancement and SARS-CoV-2 Vaccines and Therapies. Nat Microbiol 2020;5:1185-91.
8. Niotis A, Manios K, Dimas O, Tsiambas E. SARS-CoV-2 infection in breast carcinoma patients. JBUON 2021;26:1688-9.
9. Al-Maweri SA, Halboub E, Warnakulasuriya S. Impact of COVID-19 on the early detection of oral cancer: A special emphasis on high risk populations. Oral Oncol 2020;106:104760.
10. Tsounis D, Manaios L, Tsiambas E, Spyropoulou D. COVID-19 in pancreatic carcinoma patients. JBUON 2021;26:1689-90.
11. Wu A, Peng Y, Huang B. Genome Composition and Divergence of the Novel Coronavirus (2019-nCoV) Originating in China. Cell Host Microb 2020;27:325-8.
12. da Silva SJR, da Silva CTA, Mendes RPG, Pena L. Role of Nonstructural Proteins in the Pathogenesis of SARS-CoV-2. J Med Virol 2020;92:1427-9.
13. Chen L, Zhong L. Genomics functional analysis and drug screening of SARS-CoV-2. Genes Dis 2020;7:542-50.
14. Finkel Y, Mizrahi O, Nachshon A et al. The coding capacity of SARS-CoV-2. Nature 2021;589:125-30.
15. Coutard B, Valle C, de Lamballerie X, Canard B, Seidah NG, Decroly E. The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade. Antiviral Res 2020;176:104742-47.
16. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. Cell 2020;181:81-92.e6.
17. Lukassen S, Chua RL, Trefzer T. SARS-CoV-2 Receptor ACE2 and TMPRSS2 Are Primarily Expressed in Bronchial Transient Secretory Cells. EMBO J 2020;39: e105114-18.
18. Ge XY, Li JL, Yang XL et al. Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. Nature 2013;503:535-8.
19. Tsiambas E, Papanikolaou V, Chrysovergis A et al. Coronavirus in Hematologic Malignancies: Targeting Molecules Beyond the Angiotensin-Converting Enzyme 2 (ACE2) Wall. Pathol Oncol Res 2020; 26: 2823-5.

20. Tsiambas E, Chrysovergis A, Papanikolaou V, Mastronikolis N, Ragos V, Kavantzas N. Chromosome X riddle in SARS-CoV-2 (COVID-19) - related lung pathology. Pathol Oncol Res 2020;26:2839-41.
21. Ali J. Genetic etiology of oral cancer. Oral Oncol 2017;70:23-8.
22. Grégoire V. Squamous cell carcinoma of the head and neck: EHNS–ESMO–ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010;21:184-6.
23. Reder H. Genetic alterations in human papillomavirus-associated oropharyngeal squamous cell carcinoma of patients with treatment failure. Oral Oncol 2019;93:59-65.
24. Riju J, Tirkey AJ, Mathew M et al. Analysis of Early Impact of COVID-19 on Presentation and Management of Oral Cancers-an Experience from a Tertiary Care Hospital in South India. Indian J Surg Oncol 2021;5:1-8.
25. Rygalski CJ, Zhao S, Eskander A et al. Time to Surgery and Survival in Head and Neck Cancer. Ann Surg Oncol 2021;28:877-85.
26. Hande A, Sonone A, Gadbail A, Gawande M, Patil S, Sharma P. Modalities to restrain the progression of oral potentially malignant diseases and oral squamous cell carcinoma in COVID-19 pandemic. Oral Oncol 2021;114:105072-8.
27. Dolan S. What is the impact of COVID-19 on head and neck squamous cell carcinoma patients? Evid Based Dent 2020;21:52-3.
28. Denaro N, Merlotti AM, Merlano MC, Russi E. Coronavirus disease 19 (COVID-19) during chemoradiation for locally advanced oropharyngeal squamous cell carcinoma (LA-OPSCC). Oral Oncol 2020;107:104801-8.
29. Sarode SC, Sarode GS, Sengupta N, Kumar Sharma N, Patil S. Biological behavior of oral squamous cell carcinoma in the background of novel corona virus infection. Oral Oncol 2020;110:104781.
30. Sacconi A, Donzelli S, Pulito C et al. TMPRSS2, a SARS-CoV-2 internalization protease is downregulated in head and neck cancer patients. J Exp Clin Cancer Res 2020;39:200-9.
31. Martelli-Júnior H, Machado RA, Martelli DRB, Andrade MC, Coletta RD. Oral cancer and ACE2 receptor of SARS-CoV-2. Oral Oncol 2020;108:104920.
32. Guerini-Rocco E, Taormina SV, Vacirca D et al. SARS-CoV-2 detection in formalin-fixed paraffin-embedded tissue specimens from surgical resection of tongue squamous cell carcinoma. J Clin Pathol 2020;73:754-57.