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Is the oral cavity a reservoir for prolonged SARS-CoV-2 shedding?

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ABSTRACT

Limited knowledge about the contagiosity and case fatality rate of COVID-19 as well as the still enigmatic route of transmission have led to strict limitations of non-emergency health care especially in head and neck medicine and dentistry. There are theories that the oral cavity provides a favorable environment for SARS-CoV-2 entry and persistence which may be a risk for prolonged virus shedding. However, intraoral innate immune mechanisms provide antiviral effects against a myriad of pathogenic viruses. Initial hints of their efficacy against SARS-CoV-2 are surfacing. It is hypothesized that intraoral immune system activity modulates the invasion pattern of SARS-CoV-2 into oral cells. Thus, the significance of intraoral tissues for SARS-CoV-2 transmission and persistence cannot be assessed.

The underlying concept for this hypothesis was developed by the critical observation of a clinically asymptomatic COVID-19 patient. Despite a positive throat swab for SARS-CoV-2, molecular pathologic analysis of an oral perisulcular tissue specimen failed to detect SARS-CoV-2 RNA. More research effort is necessary to define the true origin of the contagiosity of asymptomatic COVID-19 patients.

Introduction

The ongoing SARS-CoV-2 pandemic has dramatically affected the world's economy and health care systems. After the first reports of COVID-19 cases in Wuhan (China) it became evident that due to the high contagiosity of COVID-19 transmitted by virus laden droplets [1,2] and/or even airborne viral particles in aerosols [3], dentists and head and neck health care providers have one of the highest risks of SARS-CoV-2 exposure, infection and dissemination [4,5]. In order to eliminate superspreading events originating from SARS-CoV-2 positive healthcare personnel, the World Health Organization has recommended to limit medical treatment involving the throat and oral cavity to medical emergencies [6]. The current discussion about the advantages and pitfalls of head and neck health care restrictions as a reasonable means to curb the spread of SARS-CoV-2 is mainly driven by expert opinion, but true evidence is gradually emerging. However, there are various reports of health care providers getting infected managing the care of COVID-19 patients [7].

The true shedding duration of potentially infectious SARS-CoV-2 particles from the upper respiratory tract and the oral cavity by acutely or formerly infected patients remains unknown and seems to be variable [8]. This knowledge would be vital to estimate at what time formerly SARS-CoV-2 positive infected patients can return to dental and head and neck physicians' offices safely to get vital but non-emergency treatment.

Early COVID-19 research has identified the upper respiratory tract (nose, naso- and oropharynx) as the primary site of SARS-CoV-2 entry and replication [9]. Nasal and olfactory epithelial cells seem to be of crucial importance for SARS-CoV-2 invasion and dissemination [10]. Recent reports have suggested that epithelial cells of the oral cavity may be extremely susceptible to SARS-Cov-2 infection. Oral epithelial cells exhibit a high expression of the receptors for cellular entry of SARS-CoV-2, angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serin 2 (TMPRSS2) [11,12]. Furthermore, periodontal pockets and crevices as well as the gingival sulcus are suspected to provide favorable conditions for virus replication and maintenance [13,14]. There are theories that synergistic effects of high expression of virus receptors and the lytic activity of periodontal bacteria might promote early and prolonged SARS-CoV-2 colonization of the oral cavity [13,14]. These ideas might be corroborated by topical literature stating that saliva samples have been tested positive for SARS-CoV-2 RNA before clinical symptoms appear [15] and remain highly positive for an extended period of time even after symptom relief [16]. The presence of ACE2 and TMPRSS2 expression in salivary glands has been reported [17]. These findings

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could imply that the oral cavity is the key area for SARS-CoV-2 transmission.

On the other hand, the oral mucosa generates very high levels of defensins, cathelicidins and other antiviral agents [18,19] the efficacy of which against SARS-CoV-2 has been reported [20]. A myriad of immunologic mechanisms ensure a powerful barrier function of the oral cavity against invading pathogens.

Hypothesis

The above mentioned reports of increased susceptibility of oral epithelial cells for SARS-CoV-2 invasion, a high viral load within saliva samples and theories of favorable conditions for SARS-CoV-2 maintenance in gingival crevices raise the following research question: are intraoral tissues a safe haven for long term SARS-CoV-2 persistence?

Intraoral innate immune system activity and the presence of various antiviral agents suppress the proliferation of pathogenic viral strains. It is hypothesized that this environment modulates the invasion pattern of SARS-CoV-2 into intraoral cells. Therefore the importance of oral tissues for SARS-CoV-2 transmission and prolonged shedding can neither be inferred nor predicted.

Case study

A 25-year old female patient was tested positive for SARS-CoV-2 infection 6 days after confirmed contact with a symptomatic patient by throat swab (April 8th 2020). After initially mild symptoms (low fever and cough) her condition deteriorated over 10 days. She reported impaired breathing, dizziness and fatigue. The fever remained low and oxygen saturation remained above 95% so that hospitalization was unnecessary. Self-reported improvement of her situation started 14 days after symptom onset. Throat swabs on April 22nd 2020 (14 days after initial positive testing) and on April 29th 2020 (21 days after initial testing) remained positive and quarantine for another ten days was advised.

On May 4th she presented to the clinic because of progressive dental pain. Clinical and radiological testing revealed that the first upper right molar showed external resorption and extraction was advised. After informed consent the tooth was extracted with respect to all recommended safety precautions for the treatment of tentatively SARS-CoV-2 positive patients (FFP-3 masks, face shield, protective full body gowns, sterile gloves, active room air circulation, intensive disinfectant application, oral disinfectant rinse). During extraction of the tooth, tissue biopsies of gingival keratinized sulcular tissues and subepithelial connective tissues were obtained for SARS-CoV-2 testing. It was hypothesized that viral RNA could be extracted from the biopsy material if the theory of high SARS-CoV-2 susceptibility of oral tissues and periodontal pockets was true. The described patient was considered to be positive for SARS-CoV-2 according to the results of throat swabs and with respect to the available clinical experience with COVID-19.

The tissue specimens were stored in formalin and analyzed histologically. The histopathological examination of the specimens showed regular oral keratinized epithelium with underlying connective tissue. RNA extraction was performed according to established standards [21]. In total, RNA in a concentration of 64 ng/μl could be gathered from the tissue biopsies. For further analysis, real-time RT-PCR analysis targeting der SARS-CoV-2 E gene, using an adopted in-house method according to a previously published protocol [9], was performed on the Applied Biosystems 7500 Real-Time PCR System. In the gingival and connective tissue biopsies, no SARS-CoV-2 RNA was detectable in this PCR assay. Informed consent and publication permission for the case report were obtained from the patient.

Discussion

The overwhelming momentum of the COVID-19 pandemic has created unexpected challenges for medical specialties with increased exposure to the upper aerodigestive tract (anesthesiology, otorhinolaryngology, oral and maxillofacial surgery, ophthalmology and dentistry). Limited knowledge about the infectivity, the duration of contagiosity, the clinical course and case fatality rate of COVID-19 together with steadily increasing numbers of infected patients have urged professional organizations and the World Health Organization to recommend the basically indefinite (after the pandemic) deferral of non-emergency medical treatment [4,6,22,23]. This approach involves a difficult triage system and a systematic reevaluation algorithm for affected patients to detect disease progress and induce therapy. Furthermore, physicians are confronted with the ethical dilemma to withhold treatment from patients in potential need. In order to prevent exacerbation of non-emergency medical problems and to, COVID-19 patients should be enabled to regain access to elective medical care as soon as possible a prerequisite for which is discontinued virus shedding.

Head and neck health care providers are highly exposed to potentially infectious patient material. Several reports have hypothesized that the oral cavity may provide an ideal medium for long term SARS-CoV-2 transmission and persistence [13,14] due to possibly favorable and synergistic conditions in periodontal pockets, a high density of SARS-CoV-2 docking molecules in oral epithelial cells [11] and the detection of high viral loads in saliva [24]. Furthermore, reports of concomitant oral mucosal lesions during active COVID-19 infection have created alertness about the tentative increased susceptibility of oral tissue cells to SARS-CoV-2 [25]. These findings have sparked the discussion whether medical procedures involving the oral cavity can be resumed safely at all during the active pandemic [6].

All the mentioned studies oversee the powerful antiviral effects of intraoral immunologic structures. The oral cavity is one of the primary contact areas of the immune system to pathogens and serves an important barrier function [26]. The transmission of various viruses, such as human immunodeficiency virus (HIV), Herpes virus (HSV) and SARS-CoV-1 can be inhibited by antiviral agents secreted into or produced within the oral cavity [27]. It can thus be inferred that these mechanisms play a role in SARS-CoV-2 defense and primary evidence has been provided [19,20,28]. Scientific investigations prove that intraorally available immunogenic peptides are a potent weapon against previously discovered pathogenic coronaviruses like SARS-CoV-1 and middle eastern respiratory syndrome (MERS) - CoV [29,30].

The above described case study provides molecular pathologic proof that oral sulcular epithelial cells and their underlying connective tissue were free of detectable SARS-CoV-2 RNA despite a positive throat swab in a clinically symptom-free COVID-19 patient. To the best of the authors' knowledge this is the first report of SARS-CoV-2 diagnostics involving human oral tissue specimens. In the examined patient there was no sign of sustained virus persistence in the periodontal environment. The integrity of the oral tissues was not affected. This observation led to the hypothesis that the particular immunogenic intraoral environment may alter the local cell invasion mechanisms of SARS-CoV-2. The true infection risk for COVID-19 originating from oral tissues can therefore not be predicted.

The presented hypothesis conceived on the basis of the presented molecular pathologic results is in contrast with previously published theories [13,14].

Conclusion

Inherent immunologic mechanisms within the oral cavity may be a useful tool against SARS-CoV-2 invasion. The prolonged contagiosity of oral tissues cannot be presumed based on the currently available knowledge.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.110419.

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