

Hyperactivated Mast Cells COVID-19 Oral Pathology Etiology Hypothesis

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Summary

COVID-19 patients with oral SARS-CoV-2 infections can develop multiple oral manifestations including tongue swelling, burning sensation in the mouth, angular cheilitis, vasculitis, Kawasaki-like oral symptoms, erythema multiforme-like symptoms, enanthema, and for patients with prolonged prone positioning while on a mechanical ventilation device acute onset macroglossia. Herein, we propose that these oral symptoms may result from histamine and inflammatory molecules released by hyperactivated mast cells in response to localized SARS-CoV-2 infections. For acute onset macroglossia, histamine associated vasoconstrictions combined with prolonged prone positioning while on mechanical ventilation results in vascular malformations and inadequate fluid drainage. Treatments consistent with this mast cell hypothesis may provide benefits to COVID-19 patients with these oral symptoms.

Abbreviations

COVID-19	Coronavirus Disease 19
COX-2	cyclooxygenase-2
NF- κ B	nuclear factor kappa B
PGE ₂	prostaglandin E2
PTGS2	prostaglandin-endoperoxide synthase 2
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
TACE	(TNF- α)-converting enzyme
TNF- α	Tumor Necrosis Factor alpha

Abstract

COVID-19 patients with oral SARS-CoV-2 infections can develop multiple oral manifestations including tongue swelling, burning sensation in the mouth, angular cheilitis, vasculitis, Kawasaki-like oral symptoms, erythema multiforme-like symptoms, enanthema, and for patients with prolonged prone positioning while on a mechanical ventilation device acute onset macroglossia. Herein, we propose that these oral symptoms may result from histamine and inflammatory molecules released by hyperactivated mast cells in response to localized SARS-CoV-2 infections. For acute onset macroglossia, histamine associated vasoconstrictions combined with prolonged prone positioning while on mechanical ventilation results in vascular malformations and inadequate fluid drainage. Treatments consistent with this mast cell hypothesis may provide benefits to COVID-19 patients with these oral symptoms.

Keywords: COVID Tongue, Mast cells, Macroglossia, Acute onset macroglossia

Introduction

SARS-CoV-2 causes changes of oral mucosa in 11.7% of COVID-19 patients [1]. Oral manifestations can include tongue swelling, burning sensation in the mouth, angular cheilitis, vasculitis, Kawasaki-like oral symptoms, erythema multiforme (EM)-like symptoms, enanthema, and acute onset macroglossia for patients with prolonged

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prone positioning while on a mechanical ventilation device [1-5]. Mast cell hyper-activation has been previously proposed to contribute to COVID-19 symptoms and disease progression [6-8]. Patients may have additional non-oral symptoms [9]. Treatments consistent with this mast cell hypothesis may provide benefits to COVID-19 patients with these oral symptoms.

Hypothesis

We propose that oral SARS-CoV-2 infection results in mast cell hyper-activation with release of histamine and inflammatory molecules. Histamine and inflammatory molecules released from mast cell may be key contributors to the etiology of the listed oral symptoms. For acute onset macroglossia, histamine associated vasoconstrictions combined with prolonged prone positioning while on mechanical ventilation may result in vascular malformations and inadequate venous fluid drainage.

SARS-CoV-2 can infect oral tissues [10,11]. The angiotensin-converting enzyme 2 (ACE2) is the cellular receptor for the SARS-CoV-2 Spike protein which is activated by proteolytic cleavages by transmembrane protease serine 2 (TMPRSS2) and sometimes furin. ACE2 and TMPRSS2 expression are detected in the stratified squamous epithelium of the dorsal tongue [12] and gingiva [13]. ACE2, TMPRSS2, and furin are expressed in taste bud-derived cultured cells [13]. SARS-CoV-2 infection of salivary glands has been detected [10,11]. In some COVID-19 patients, SARS-CoV-2 directly infects the oral cavity. Immune responses to SARS-CoV-2 infections can include the activation of mast cells [7,8,14,15].

Mast cells can be activated by Fc receptor bound antibodies binding to virions or possibly viral proteins. The SARS-CoV-2 nucleocapsid protein has been predicted to bind to the prostaglandin-endoperoxide synthase 2 (PTGS2)/cyclooxygenase-2 (COX-2) promoter upregulating COX-2 resulting in elevated prostaglandin E₂ (PGE₂) levels [16]. Elevated levels of PGE₂ can cause hyper-activation of mast cells [17]. Another potential pathway for upregulating COX-2 includes the SARS-CoV-2 Spike protein interacting with Tumor Necrosis Factor alpha (TNF- α)-converting enzyme (TACE) inducing TNF- α production like observed for the SARS-CoV-1 Spike protein [18]; the nuclear factor kappa B (NF- κ B) pathway is activated by inducing I- κ B α degradation [19,20]. TNF- α stimulates COX-2 expression [21]. There may be more than one pathway by which SARS-CoV-2 infections are hyper-activating mast cells.

Proposed Adjunctive Treatments for Evaluation

Treatments targeting hyper-activated mast cells, may reduce or eliminate symptoms associated with elevated histamine, elevated inflammatory molecules, and vasoconstrictions [7,22-24]. Treatments consistent with the mast cell hypothesis associated with preliminary reports of clinical efficacy in COVID-19 patients include celecoxib [25,26], famotidine [6,26], cetirizine [27], dexchlorpheniramine [27], and montelukast [28], and aspirin [29,30]. Note that concomitant administration of celecoxib and dexamethasone is contraindicated. These treatments may provide benefit to individuals experiencing COVID-19 the oral manifestations associated with hyperactivated mast cells, elevated histamine levels, and induced vasoconstrictions. The effective dosages for antihistamines targeting immune cells may be different from other therapeutic applications of these

treatments [6,31]. Evaluation of these treatments and treatment combinations on COVID-19 patients with relevant oral symptoms (swelling, burning sensations, vasculitis, Kawasaki-like oral, EM-like, enanthema, and acute onset macroglossia) in case reports and case series can inform subsequent randomized controlled clinical trials for treating oral symptoms in COVID-19 patients.

Distribution Statement

Approved for public release. Distribution is unlimited.

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Data Availability Statement

No datasets were generated or analyzed during the current study.

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