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May macroglossia in COVID-19 be related not only to angioedema?

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ABSTRACT

SARS-CoV-2 infection can lead to a variety of clinical manifestations. The occurrence of tongue swelling has recently reported in severe cases of COVID-19, and angioedema has suggested as the causative mechanism. Several factors, such as genetic predisposing factor and angiotensin-converting enzyme inhibitors (ACEI) therapies, have proposed to induce angioedema, especially as concerns patients requiring ICU treatments. Nevertheless, the question is still debated and other causes not yet recognized should be considered.

Here we present a case of macroglossia occurred in a patient deceased for COVID-19 disease, who had no family history of angioedema and did not receive ACEI as antihypertensive drug. Histological and immune-histochemical analysis revealed tongue muscle atrophy with infiltrating macrophages suggesting repair mechanisms, as seen in nerve injury recovery. These new pathological findings may open new fields of study on the pathogenesis of SARS-CoV-2.

Introduction

The main pathological features of the coronavirus disease (COVID-19) are pulmonary and cardiovascular involvement, nevertheless the infection with SARS-CoV-2 may lead to multisystem disease [1], affecting different organs, both directly or indirectly [2–5]. SARS-CoV-2 entry into host cells is mediated by specific binding to the angiotensin-converting enzyme 2 (ACE2) receptors [6], thus the multiorgan pathology could be enabled by the wide distribution of ACE-2 receptors in different tissues.

The epithelial cells of the tongue express high level of ACE2, suggesting possible explanation for taste disturbances, such as ageusia or dysgeusia, and tongue mucosal lesions described in COVID-19. Cases of macroglossia have recently been reported in COVID-19 patients [7,8]. Macroglossia is an abnormal enlargement of the tongue, which can be congenital or acquired. Angioedema is among the conditions that may result in macroglossia. A well known cause of angioedema is the ACE inhibitors (ACEI) treatment, through an uncommon side effect on the angiotensin-renin vascular control system, by a bradykinin-mediated pathway. In this consideration, SARS-CoV-2 dysregulation of ACE2 has been proposed as the mechanism explaining the occurrence of tongue swelling in COVID-19 patients [9].

Here we present a case of macroglossia, occurred in a patient with severe COVID-19 disease. Post-mortem histopathological analysis highlights new findings in the pathogenesis of SARS-CoV-2.

Case presentation

A 52-year-old African man, with a medical history of hypertension, presented to the emergency room with fever, dyspnea, and difficulty in speaking. He referred returning from a trip to Nigeria 16 days earlier, and a 7-day history of fever. SARS-CoV-2 RT-PCR assay from oropharyngeal swab was performed, and tested positive. Computed tomography (CT) showed severe COVID-19-associated pneumonia. VMK 40% and PEEP were initiated. Due to worsening in respiratory function (PaO_2:FiO_2 ratio <100 mgHg) on day 3 the patient was admitted to the intensive care unit and, on day 5, tracheal intubation was performed. Despite medical management, in the next few days his clinical conditions quickly worsened thus alveolar-recruitment maneuvers were used on day 7. Swelling of the tongue occurred on day 4 after the admission and an allergic reaction to antibiotics was assumed, even though neither itchiness nor cutaneous rash were present. This condition was not responsive to steroids and histamine blockers, and the patient had no known history of allergies, or any family history of heredi-

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ICU, Intensive Care Unit; ACE2, angiotensin-converting enzyme 2.

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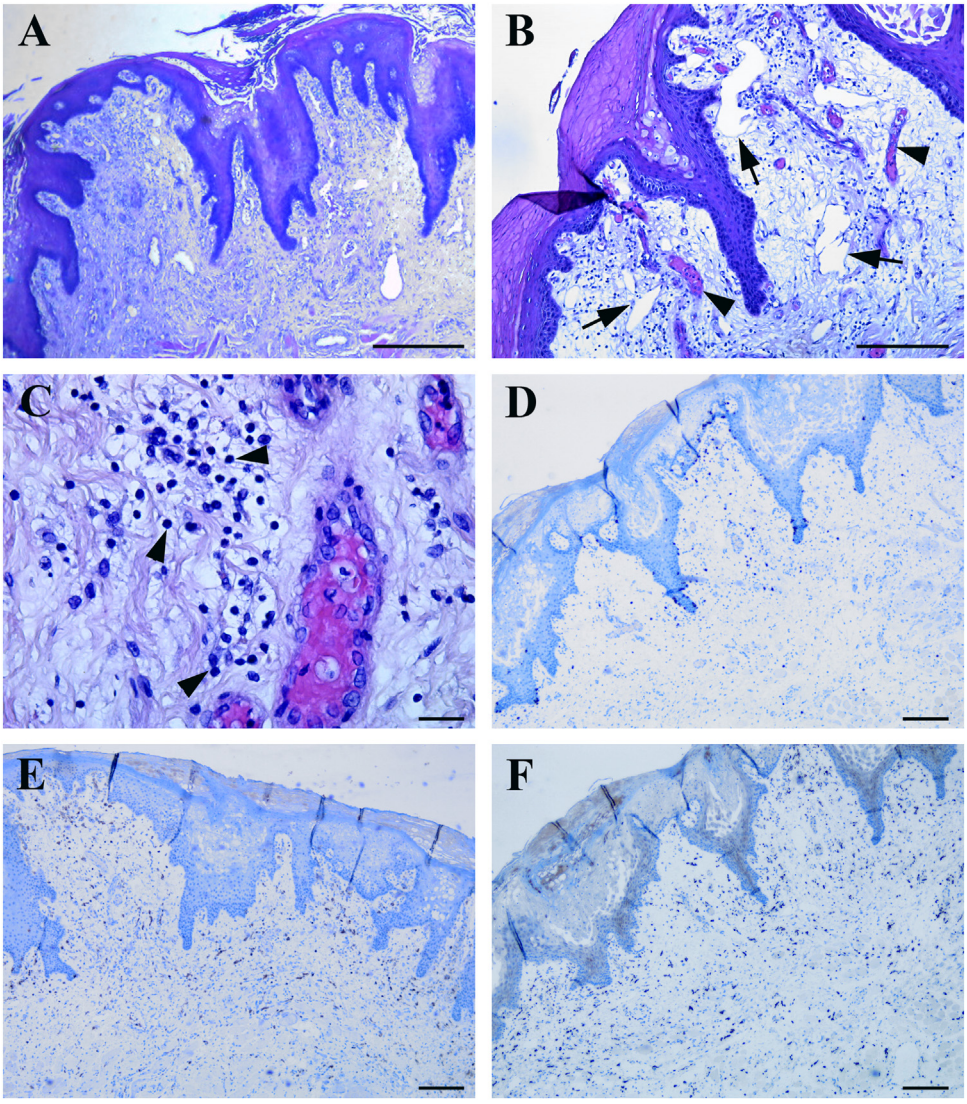

Fig. 1. Histology and immunohistochemistry of tongue mucosa. (A–C) Hematoxylin–Eosin (H&E) stained mucosal sections. (A) Representative micrograph showing the keratinized epithelium with fungiform papillae and underlying lamina propria. (B) In sub-epithelial layer marked dilatation of lymphatic vessels (arrows) and congestion of vascular structures (arrowheads) is present. (C) Inflammatory cells (arrowheads) were not associated to vasculitis. (D–F) Immune-histochemical characterization of inflammatory infiltrate (brown stained cells). Lymphocytes, composed by few cytotoxic CD8+ T cells (D) and numerous CD4+ T cells (E), are visible in sub-epithelial layer and scattered in the lamina propria. Numerous CD68+ macrophages are present (F).
Scale bars: A = 400 μm; B, D–F = 100 μm; C = 14 μm.

tary angioedema. The occurrence of angioedema, even as a result of patient prone positioning was supposed, so semi-sitting position was adopted. On day 8 otorhinolaryngology consultation with flexible fiberoptic examination showed lingual edema, with unobstructed larynx and trachea. Due to worsening of macroglossia the patient was treated with Icatibant (Firazyr, 30 mg), for suspicion of bradykinin-mediated angioedema. The condition of patient tongue not improved and, computed tomography (CT-scan) of the head and neck, performed on day 13, revealed a complete obstruction of oropharynx and nasopharynx. The tongue appeared increased in volume and hypodense, and did not show any underlying neoplastic process. Measurement of C4 serum levels (performed to screen for C1-INH deficiency) showed normal values, nevertheless Berinert was administered (1500 UI). On day 14 patient's general conditions further worsened and he died for bilateral interstitial pneumonia associated to bronchopneumonia and pleuritis, as assessed by complete post-mortem examination. At time of death the macroglossia was severe, with the tongue completely protruding beyond the mouth.

At autopsy, a portion of the anterior third of the dorsal surface of the tongue was taken, to examine the pathological aspect underlying the enlargement. Histological examination of hematoxylin stained sections revealed preserved fungiform papillae (Fig. 1A). The lamina propria was edematous, characterized by numerous congested vascular structures and dilatation of lymphatic vessels (Fig. 1B). Inflammatory infiltrate was mild, localized in sub-epithelial layer, and was not associated to lichenoid pattern or vasculitis (Fig. 1C). Cells of the inflammatory infiltrate mostly consisted in lymphocytes T CD4+ cells (Fig. 1E) and less cytotoxic CD8+ T cells (Fig. 1D), and CD68 positive macrophages (Fig. 1F).

The most striking findings in our case concerned the lingual muscular tissue, which appeared atrophic and replaced by collagen and fat (Fig. 2A). Masson trichrome stain highlighted septal and endomysial fibrosis dissociating the myofibers, which become disorganized and reduced in size on cross-sectional area (Fig. 2B). Many infiltrating macrophages CD68+ were present around muscle fibers and in the perimysium, or scattered throughout the damaged

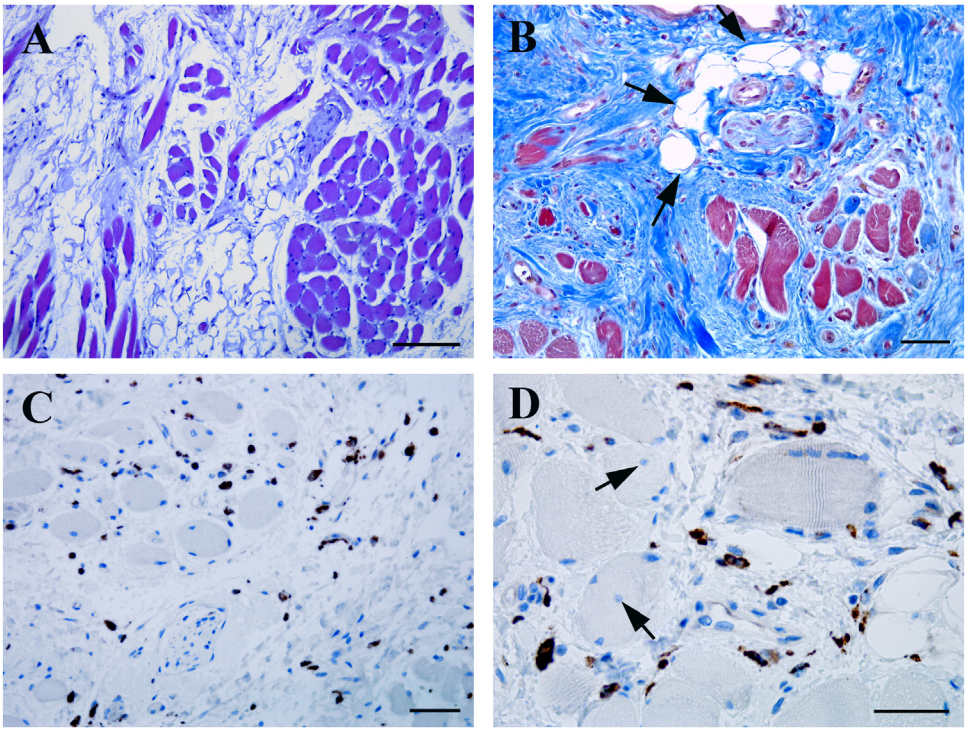

Fig. 2. Histology and immunohistochemistry of lingual muscle. (A) Atrophic appearance of muscle fibers characterized by increased connective tissue and fat accumulation (H&E stain). (B) Masson's trichrome staining of tongue sections highlights extensive muscle fibrosis with abundant collagen deposition (blue stained) around atrophic and irregular muscle fibers (red stained); fatty replacement is also visible (arrows). (C) CD68 immune-staining shows the presence of numerous macrophages (brown stained) infiltrating the tongue muscle. (D) Higher magnification image shows numerous CD68 positive macrophages in the endomysium surrounding muscle fibers and in sites of extracellular matrix deposition. Note the presence of centrally located nuclei (arrows).
Scale bars: A = 100 μm; B, C = 28 μm; D = 14 μm.

areas (Fig. 2C, D). Of note, damaged myofibers frequently displayed central nuclei (Fig. 2D).

Discussion

Induction of angioedema in COVID-19 may be a side effect caused by ACE2 receptors downregulation due to SARS-CoV-2 binding [9]. This effect could be further amplified in hypertensive patients treated with ACEI, or genetically predisposed patients [10]. Our patient did not receive ACEI as antihypertensive drug; he was treated with amlodipine besylate therapy, which, belonging to the calcium channel blockers (CCBs), is not among drugs favorable to angioedema development. Moreover, the patient was treated with Icatibant and Berinert, supporting the idea that in this case the angioedema could not be bradykinin-mediated or due to C1-INH deficiency.

We believe that tongue swelling may depend solely on SARS-CoV-2 infection, although as a rare manifestation. In this agreement similar cases of tongue edema and protrusion have described in COVID-19 patients not treated with ACEIs or angiotensin receptor blockers, with no hereditary angioedema and not responsive to antihistamines or corticosteroids [11,12].

Based on histological findings, we propose that even other mechanisms, besides angioedema, can contribute to the onset of macroglossia in SARS-CoV-2 infection.

We found muscle atrophy and fatty accumulation, a pattern similar to tongue pseudohypertrophy in patients with amyotrophic lateral sclerosis [13]. Interestingly we also observed elevated number of central nuclei, which, together with muscle fibers atrophy, are pathological markers of nerve injury or altered neuro-muscular junctions [14]. In addition, we found numerous infiltrating macrophages, a critical component of muscle recovery from nerve injury [15]. Muscle fibers atrophy, inflammatory cells infiltration and nerve pathologic changes have very recently described in autoptic samples from patients dying of COVID-19, thus supporting our observations [16]. Neuronal damage has been recognized as a COVID-19 complication [17] and it has been suggested that the taste dysfunction arises from specific cranial nerve involvement, by direct invasion of the SARS-CoV-2 virus into the olfactory and trigeminal nerve cells, or by a demyelinating reaction in olfactory neurons [18]. Thus, we propose that macroglossia may also be related to SARS-CoV-2-induced neuronal disorders, having the patient speaking difficulties before the onset of tongue swelling.

In conclusion, we highlights unexpected muscular atrophy in COVID-19 macroglossia. This finding, in addition to edema, could be directly related to SARS-CoV-2 infection; in particular, neuromuscular injury should be further investigated.

Authors' contributions

D.C. and L.F., interpretation of data and writing the manuscript; F.D.N. and D.C., post-mortem examination and histopathological diagnosis R.N., investigation. All authors have read and agreed to the published version of the manuscript.

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Competing interests

None declared.

Ethical approval

Not required.

Institutional review board statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Clinical Research Ethics Committee (approval number: n° 9/2020).

Informed consent statement

Informed consent was waived by the Ethics Commission due to public health outbreak investigation.

Data availability statement

All relevant data are within the manuscript.

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