Tongue microbiota and pathological processes: a pilot autopsy study

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Resumen

Context: Human general health may be mirrored in oral changes, and oral lesions can hallmark systemic diseases. Diverse pathological processes and numerous infectious agents have been described in the human oral cavity. Autopsy reports of the association among oral pathogens, tongue pathological changes, and systemic diseases are still lacking.

Aim: To describe pathological processes and infectious agents found in the tongues of necropsied patients, and comment the data from coexistent systemic disease.

Design: Cross sectional study.

Setting and Participants: Twenty-four complete autopsies of adults were randomly selected in a Brazilian University Hospital.

Main Outcomes Measures: After macroscopic evaluation, the tongues were longitudinally sectioned and the tissue samples were submitted to the histological routine.

Results: The histopathology changes were: hydropic degeneration (83.3%), atrophy (75%), inflammation (70.8%), necrosis with ulceration (70.8%), hypertrophy (58.3%), necrosis without ulceration (16.6%) and arteriolar hyalinosis (4.2%). The microbiota consisted of: bacteria (54.2%), Candida sp (25%), Cryptococcus sp (4.2%) and Malassezia furfur (4.2%). Bacteria were found on the tongues from all the patients with rheumatic cardiopathy or pyelonephritis, in 44.4% of the patients with bronchopneumonia and in 40% of the patients with esophagitis. Half of AIDS patients presented Candida sp hyphae associated with tongue inflammation, necrosis and ulceration.

Conclusions: Although not always associated to gross lesions, the tongue microbiota can cause pathological processes. As oral pathology has been associated with systemic diseases, workers in health care should develop a higher awareness about the role of tongue changes in the general health.

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Introduction

There is a close relationship between the general health and oral mucosa disturbances, and in numerous conditions the oral changes may be indicative signs of systemic diseases [1-3]. Moreover, agents of common oral diseases may play a role in the mechanisms of main general risk factors and causes of human death [4]. Diverse infectious agents and pathological processes that affect the human tongue have been reported [5, 6], and associations between the microbiota and tongue lesions have been described in autopsied patients with acquired immunodeficiency syndrome (AIDS) [7, 8]. However, there are rare autopsy reports about the tongue microbiota and associated gross and microscopical changes, as well as about descriptions of the coexistent systemic conditions [9].

General disorders have oral manifestations, which may precede the systemic changes. In some systemic diseases, the infectious agents may trigger oral lesions that represent the unique clinical finding [10], and the tongue microbiota may contribute to the development both of common and severe diseases as dermatitis, nephritis, arthritis, pneumonitis, endocarditis, atherosclerosis and coronariopathy [3-5].

The main objective of this pilot study is to evaluate the macroscopic and microscopic changes on the tongues from autopsied adults, and to associate the data with the infectious agents found in this organ.

Participants and methods

The study was approved by the Ethics Committee of the University of Uberaba (UNIUBE), Uberaba-MG, Brazil, and was conducted to analyze records of complete autopsies from the Federal University of Triângulo Mineiro (UFTM), Uberaba-MG, Brazil. Twenty-four records were randomly selected from the total of adult autopsies performed in a period of one year. Inclusion criteria of the study were: 1) complete necropsies, with the entire tongue, or at least the posterior third of the organ suitable for analysis; 2) respective medical charts with patient's age, gender, color, and body mass index (BMI), clinical data and complementary exams. Exclusion criteria consisted in discard the patients with concomitant local factors that could change the results of the study, as the example of individuals with nasogastric tubes or some evidence of oral trauma.

Twenty-four tongues were then submitted to macroscopic and microscopic evaluations. After the macroscopic exam, the tongues were longitudinally sectioned along the median sulcus, and 0.5cm thick fragments were taken for analyses. The samples were submitted to histological procedures and the slides were stained by hematoxylin-eosin (HE), Grocott's methenamine silver (Grocott), periodic acid Schiff (PAS), mucicarmine, and picrosirius.

The microscopy study was performed in samples from longitudinal sections of the midline of the organ. The morphological analysis of the tongue epithelium was done to identify pathological processes such as degeneration, necrosis, inflammation, and cell growth disorders. The tongue microbiota was assessed on the slides stained with HE, picrosirius, PAS, Grocott, and mucicarmine. Infection by Human papilloma virus (HPV) was suspected in one case, and the samples were also submitted to immunohistochemistry study with avidin-biotin-peroxidase complex and anti-HPV antibodies (Dako).

As the kinetic of the death can vary among the microorganisms found in the tongue, the components of the microbiota were also compared between two groups of patients classified by the time elapsed between the moment of the death and the necropsy study (< 12 hours versus ≥ 12 hours).

Results

The patient's demographical data showed a mean age of 61 years, 16 males and 8 females, 22 white and two non-white individuals, with a mean BMI of 20.26 kg/m². The diagnoses of systemic and infectious conditions were established with basis on the clinical records, in addition to the macroscopic and microscopic necropsy data. The complete macroscopic assessment was possible in 15 tongues (62.5%) that were totally removed during autopsy, while in nine cases only the posterior third of the organ was assessed. The filiform papillae from the 15 organs showed changes. There was hypertrophy in six cases (40%) and atrophy in three cases (20%); while ulcerations were not seen on macroscopic examination (**table 1**).

Table 1. Infectious agents and macroscopic changes observed in tongue papillae from 15 adult autopsied patients

	Macroscopic changes in tongue papillae	
Infectious agents	Hypertrophy (n = 6)	Atrophy (n = 3)
Bacteria (n = 13)	5 (83.3%)	1 (33.3%)
Candida sp hyphae (n = 6)	3 (50%)	0
Cryptococcus sp (n = 1)	1 (16.6%)	0
Malassezia furfur (n =1)	0	1 (33.3%)

The microscopic study revealed mucosal lesions including: hydropic degeneration (20 cases, 83.3%), atrophy (18 cases, 75%), inflammation (17 cases, 70.8%), necrosis with ulceration (17 cases, 70.8%), hyperplasia (14 cases, 58.3%), and necrosis without ulceration (4 cases, 16.6%) as showed in **table 2**. Arteriolar hyalinosis was found in one case, coexistent with benign nephrosclerosis and renal arteriolar hyalinosis.

On the tongue samples from 13 cases (54.2%), non-classified bacteria were found by HE staining (**figure 1A**).

Table 2. Frequency of infectious agents and pathological processes disclosed by microscopic assessment of 24 tongues from adult autopsied patients

	Infectious agents			
Pathological processes	***Bacteria*** (n =13)	***Candida sp*** hyphae (n = 6)	***Cryptococcus sp*** (n = 1)	***Malassezia furfur*** (n = 1)
Mucosa inflammation	10 (76.9%)	5 (83.3%)	1 (100%)	1 (100%)
Epithelial hypertrophy	9 (69.2%)	3 (50%)	1 (100%)	1 (100%)
Epithelial atrophy	12 (92.3%)	5 (83.3%)	0	1 (100%)
Hydropic degeneration	13 (100%)	5 (83.3%)	1 (100%)	1 (100%)
Epithelial necrosis without ulceration	3 (23%)	1 (16.7%)	0	0
Epithelial necrosis with ulceration	10 (76.9%)	5 (83.3%)	1 (100%)	1 (100%)

Among the diagnoses of the 24 analyzed cases, two were pyelonephritis and two were rheumatic cardiopathy, and bacteria were detected on the tongues of them all. Tongue bacteria were also found in four (44.4%) of nine patients with bronchopneumonia and in two (40%) of five patients with esophagitis. The coexistence of tongue bacteria and Candida sp hyphae (Candida) was detected in one case (**table 3**).

Table 3. Systemic diseases and infectious agents detected in tongues from 24 adult autopsied patients

	Rheumatic (n = 2)	Pneumonitis (n = 9)	Pyelonephritis (n = 2)	Esophagitis (n = 5)	Gastritis (n = 2)	AIDS (n = 4)	Chagasic (n = 10)
Bacteria	2	4	2	2	1	1	6
(n = 13)	(100%)	(44.4%)	(100%)	(40%)	(50%)	(25%)	(60%)
Candida	0	2	1	2	1	2	1
(n = 6)	0	(22.2%)	(50%)	(40%)	(50%)	(50%)	(10%)
Crypto	0	1	0	0	0	1	0
(n = 1)	0	(11.1%)	0	0	0	(25%)	0
M. furfur	0	0	0	0	0	0	1
(n = 1)	0	0	0	0	0	0	(10%)

Candida: Candida sp hyphae; Crypto: Cryptococcus sp; M. furfur: Malassezia furfur.
Rheumatic: Rheumatic cardiopathy; Chagasic: Chagasic myocardiopathy.

Candida was found by the routine histopathological method with PAS and Grocott's staining (**figure 1B**), in six cases (24%) including: one case with bronchopneumonia; one with AIDS accompanied by bronchopneumonia and esophagitis; one with AIDS and systemic cryptococcosis; one with pyelonephritis; and one with esophagitis and gastritis. As a whole, Candida was detected in two of four patients with AIDS (50%). In one (with disseminated cryptococcosis and bronchopneumonitis), Candida, non-classified bacteria and Cryptococcus sp were seen accompanied by necrosis, severe epithelial ulceration and moderate subepithelial inflammation. Cryptococcus sp was detected by Grocott's and mucicarmine staining (**figure 1C**). Candida associated to inflammation, necrosis and severe epithelial ulceration were found in another AIDS case associated with bronchopneumonitis. One patient with AIDS had necrosis with epithelial ulceration of the tongue and a whitish papule (1.0 x 1.0cm) in the jugal mucosa close to the labial commissure. In this case, the histochemical analysis found viral inclusions (**figure 1D**) and immunohistochemistry was positive for HPV (**figure 1E**). Malassezia furfur (M. furfur) was seen on the tongue (**figure 1F**) and on the scalp samples from a chronic chagasic patient with esophageal carcinoma.

No significant difference was observed between the tongue microbiota from patients submitted to necropsy < 12 hours and ≥ 12 hours after the moment of death (p = 1), as showed in **table 4**.

Table 4. Distribution of the 24 autopsied patients, in accordance with the infectious agents and the elapsed time between the moment of the death and the autopsy

Infectious agent	**Elapsed time between the death and the autopsy**	
(Presence versus absence)	< 12 hours (n = 13)	≥ 12 hours (n = 11)
Bacteria	8 vs 5	5 vs 6
Candida sp	3 vs 10	3 versus 8
Malassezia furfur	0 vs 13	1 vs 10
Cryptococcus sp	0 vs 13	1 vs 10

Fisher's exact test, p = 1

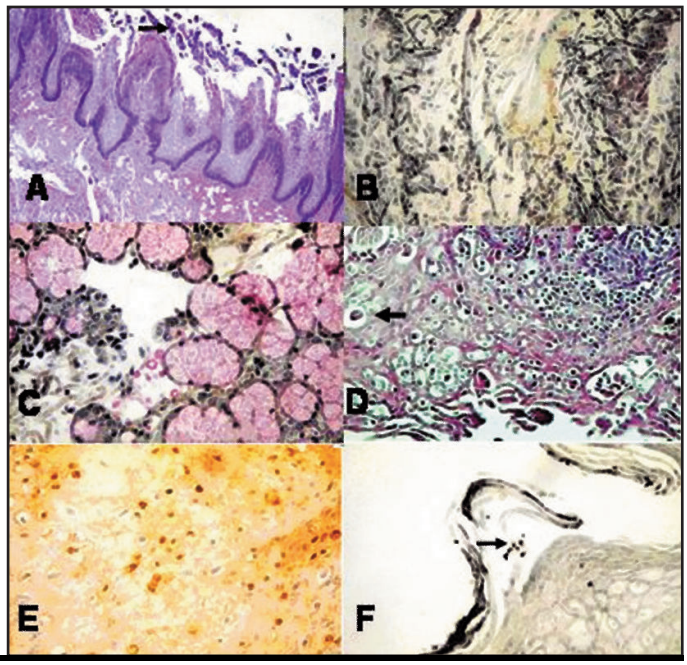

Figure 1. Histopathological findings of tongue microbiota from adult autopsied patients.
Figure 1 A. Bacteria (arrow) (Hematoxylin-Eosin, X200).
Figure 1B. Candida sp hyphae (Grocott's methenamine silver, X200).
Figure 1 C. Cryptococcus sp (arrow) (Mucicarmine, X600).
Figure 1 D. Tongue epithelium with viral inclusions (arrow), in addition to necrosis and inflammation (Hematoxylin-Eosin, X400).
Figure 1 E. Human papillomavirus (HPV) inclusions (Immunohistochemistry, X600).
Figure 1 F. Malassezia furfur (arrow) (Grocott's methenamine silver, X600).

Discussion

Over than 700 microorganisms species have been identified on the human tongue [5, 6]; however, there are few studies associating these bacteria with local lesions or systemic diseases [3-5, 10, 11]. In the present study, bacteria of the tongue coexisted with local pathological processes such as mucosal inflammation, epithelial hypertrophy or atrophy, hydropic degeneration, and epithelial necrosis. The data from this preliminary study emphasize the question of a possible correlation between tongue pathological conditions and general health. Actually, important associations among risk factors or manifestations of systemic conditions and the microbiota from teeth, dental plaques, gums, buccal and pharyngeal mucosa, and saliva have been reported [1, 3-5, 11].

Bacteria were observed on the tongue from all the patients with pyelonephritis and rheumatic cardiopathy, however, no study about the association of tongue microbiota and nephritis or rheumatic cardiopathy could be found. It is well-known that oral Streptococcus and Staphylococcus can cause rheumatic cardiopathy and endocarditis, and bacteria-related immune complexes may be deposited in the kidneys and origin nephritis. In addition, some members from other oral pathogen genera, as Corynebacterium, can cause pyelonephritis and endocarditis in immunocompetent adults [12, 13].

Deposition of immune complexes may also occur in the vascular endothelium, and cause arteriolar hyalinosis, which is more often associated with diabetes and arterial hypertension [14]. In the present study, hyalinosis was found in the tongue of a patient with essential hypertension and benign vascular nephrosclerosis.

Etiologies of esophagitis include infections caused by bacteria [15] and candidiasis [16, 17]. Among patients with esophagitis, tongue bacteria were observed in 20%, Candida in 20%, and the association of Candida and bacteria in 20% of the cases. Nevertheless, we did not find any description about the role of tongue bacteria in the development of esophagitis.

Pneumonitis is an important cause of morbidity and mortality, especially in elderly people [18]. Four out of the nine patients with bronchopneumonia presented tongue bacteria, and all were older than 59 years. Bacteria present in dental plaque are a well-known cause of aspiration pneumonitis in the elderly, at least in part due to the tongue papillary structure which favors the retention of food residues and is a reservoir for respiratory pathogens [19]. Therefore, aspiration of tongue bacteria could have a role in the genesis of the bronchopneumonia observed in these autopsied patients.

Although Candida sp can be found in the oral flora from near 60% of the normal healthy

adults, local and systemic factors as immunodepression favor overgrowth [20]. There are reports of oral lesions caused by systemic mycoses, which generally cause chronic ulcerations and are associated with immunodepression [21]. Candidiasis and infection by Cryptococcus sp have been detected on the tongue of patients with AIDS, causing inflammation and necrosis followed by chronic ulcerations [8, 22]. In one necropsied patient with AIDS, Cryptococcus sp and Candida were associated with tongue ulcerations.

M. furfur was found on the tongue and scalp of the chagasic patient with esophageal cancer. This fungus caused subepithelial inflammation and tongue ulceration. We could not find any report about the finding of M. furfur in human tongues. Fungi overgrowth was probably due to immunodepression and malnutrition caused by the malignancy and Chagas disease [23, 24]. Indeed, opportunistic infections by M. furfur and candidiasis are described in renal transplant patients under immunosuppressive therapy [25]. Infectious agents were seen on the tongues of the patients with AIDS, and one presented a lesion caused by HPV in the jugal mucous membrane. Although HPV lesions may be found in immunocompetent people, the proliferation of opportunistic agents in the oral cavity, especially on the tongue, has been found associated with immunodepression [8]. Furthermore, a higher frequency of HPV lesions in the oral cavity has also been reported in men with AIDS [26].

With base on these preliminary data, a further purpose is to study a more representative homogenized sample, which allows to extrapolate the findings to the general population. Molecular approaches must be performed to better identify the microbial agents disclosed on the tongue dorsum [6, 27-30], in addition to a multivariate analysis to verify the strength of association between the involved microorganisms and the coexistent specific pathologies.

Although the clinical significance of the present data remains to be better cleared, at least in part they may contribute to better understand the role played by tongue microbiota in health and disease.

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Conflicts of interest:

The authors have neither financial nor non-financial conflicts to declare.

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Microbiota de la lengua y procesos patológicos: estudio piloto de autopsia

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Resumen

Contexto: La salud general puede reflejarse en cambios orales, y lesiones orales pueden anunciar enfermedades sistémicas. Se han descrito procesos patológicos y agentes infecciosos en la boca humana. Todavía, faltan datos de autopsia sobre la asociación entre patógenos orales, cambios patológicos de la lengua, y enfermedades sistémicas.

Objetivo: Describir los procesos patológicos y agentes infecciosos encontrados en lenguas de pacientes sometidos a autopsia, y comentar datos de enfermedades sistémicas coexistentes.

Diseño: Estudio observacional, transversal y analítico.

Lugar y sujetos: Se seleccionaron de modo aleatorio 24 autopsias completas de adultos en un Hospital Universitario de Brasil.

Métodos y mediciones principales: Después de evaluación macroscópica, las lenguas fueran longitudinalmente seccionadas y muestras del tejido se sometieron a la rutina histológica.

Resultados: Los cambios histopatológicos fueron degeneración hidrópica (95.8%), atrofia (87.5%), inflamación (83.3%), necrosis con ulceración (70.8%), hiperplasia (58.3%), necrosis sin ulceración (25%) y hialinosis arteriolar (4.2%). La microbiota consistió de: bacterias (54.2%), Candida sp (20.8%), Cryptococcus sp (4.2%) y Malassezia furfur (4.2%). Se encontraron bacterias en todos los pacientes con cardiopatía reumática o pielonefrite, en 44.4% de pacientes con bronconeumonía y en 40% de pacientes con esofagitis. La mitad de los pacientes con SIDA presentó hifas de Candida sp, con inflamación, necrosis y ulceración de la lengua.

Conclusiones: Aunque no siempre asociada con cambios macroscópicos, bacterias de la lengua causan procesos patológicos. Como la patología bucal se relaciona con enfermedades sistémicas, obreros de la salud deben tener un mayor conocimiento sobre el papel de los cambios orales en la salud general.

Palabras clave:
Microbiota, Autopsia, Lengua, Patología, Molestias sistémicas