

Oral mucocelles: a clinicopathological study of 401 cases, emphasizing uncommon histopathological variants

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Aim: The aim of this study was to describe the clinicopathological features of an oral mucocelles series, with emphasis on the unusual histological variants. **Methods:** Between 2000 and 2019, all oral mucocelles diagnosed at a Brazilian Oral Pathology Laboratory, were analyzed. All slides stained in hematoxylin-eosin (HE) were reviewed for confirmation of diagnosis. The collected data were analyzed using the IBM SPSS Statistics software, version 24.0, obtaining the descriptive statistical analysis in absolute and relative numbers for all the described variables. **Results:** From the 6,875 oral lesions, 401 (5.83%) were mucocelles. There was a predilection for females (58.6%), and the most affected site was the lower lip (78.8%). Excision was the treatment of choice for the most patients (68.1%). Among the uncommon histological variants, the superficial mucocelles (6.2%) were the most common, and the least frequent was the clear cells changes (0.5%). In 225 (56.1%) lesions, the predominant mucus was of the myxoid type. **Conclusion:** Although most mucocelles did not represent a diagnostic challenge, they may present unusual histological variants. Thus, depending on the histological variant, other lesions, including neoplasms, should be considered in the histopathological differential diagnosis.

Keywords: Mucocelles. Pathology. Diagnosis, oral. Salivary glands, minor.



Introduction

Mucocoeles are benign pseudocystic lesions that affect the oral mucosa, which develop as consequence of extravasation of mucus from salivary glands, especially minor salivary glands¹. Clinically, the lesion appears as a painless nodule, of variable size and color, located mainly on the lower lip. The lesions occur most commonly during the second decade of life, and no gender predilection had been observed²⁻⁷.

Histologically, there are phenomena of extravasation or retention of mucus^{3-5,8,9}. The overflow mucocoeles results from the rupture of the excretory duct of the salivary gland, which consequently leads to spillage of mucus between the tissues adjacent to the gland⁶⁻¹⁰. This mucocoele has three stages of development. In the first phase, the mucus diffuses from the glandular duct to the underlying tissues, and leukocytes and macrophages, can be observed. In the second phase, also called the reabsorption phase, granulomas are formed due to the presence of numerous macrophages and eventual giant cells associated with the foreign body reaction. Then, in the third phase, a pseudo-capsule without epithelium lining will be formed around the mucosa, which is composed by a granulation tissue^{10,11}.

Retention mucocoeles most often affects the major salivary glands and are caused due to ductal obstruction, presence of sialolith, dense salivary secretion, periductal scarring or tumors^{1,10}. Histologically, the retention mucocoeles are characterized by the epithelial lining from the salivary duct¹. Because of the histopathological and clinical differences between these phenomena, only lesions resulting from the rupture of the salivary gland duct and consequent mucin leakage can be considered as mucocoeles¹².

Despite of the relatively common histopathological characteristics, mucocoeles may present morphological diversity¹²⁻¹⁴. Some unusual histopathological features have been observed, such as myxoglobulosis, papillary synovial metaplasia-like changes, dissociation of collagen fibers after mucin extravasation, superficial mucocoeles, significant reduction in the cavity lumen, and clear cell changes¹²⁻¹⁸. Usually, oral mucocoele is not a diagnostic challenge. However, these unusual microscopic features can cause misdiagnosis. Few studies have evaluated these histological variants of oral mucocoeles, especially unusual features¹²⁻¹⁸. Thus, the objective of this study was to evaluate the clinical and microscopic characteristics of a large series of oral mucocoeles (extravasation of mucus), focusing on illustrate uncommon histological features.

Materials and methods

This cross-sectional and retrospective study was approved by the Local Research Ethics Committee and complied with the Declaration of Helsinki (protocol number #99460718.8.0000.5208).

Between 2000 and 2019, all oral mucocoeles diagnosed at a Laboratory of Oral Pathology in Brazil, were selected for the study. Initially, clinical and demographic data were collected from the clinical charts, including sex and age of the patients. In relation to

the lesion, the site, mean time of duration in months, type of complaint referred by the patient, and clinical aspect and size of the lesion, were recorded. The correlation between clinical hypotheses of diagnosis and final histopathological diagnosis was classified as correct or incorrect.

All cases were microscopically reviewed on slides stained with hematoxylin and eosin (HE) by two experienced pathologists. The specimens that did not have adequate tissue for analysis were excluded. Histopathological variants were analyzed based on the study by Monteiro et al.¹⁴(2016), which are: myxoglobulosis, papillary synovial metaplasia-like changes, significant reduction in the cavity lumen, dissociation of collagen fibers after mucin extravasation, superficial mucocoeles and clear cell change. In addition, the aspect of the overlying oral mucosa (if normal, atrophic, hyperplastic, or ulcerated), the type of minor salivary glands involved (mucosa or seromucosa), the state of the glandular acini and ducts, the type of mucus (hyaline or myxoid aspect), and the aspects of the adjacent connective tissue (presence of vascular congestion or inflammatory infiltrate), were also evaluated⁸.

The criterion used to classify lesions with myxoglobulosis was based on the study of Chi et al.¹²(2011), which considered myxoglobulosis only when the globular structures involved at least 30% of the lesion. Superficial mucocoeles were classified according to Eveson¹⁷(1988), which consider the presence of subepithelial bubble containing mucin, atrophy of the superficial epithelium, possible regeneration of the epithelium through the bubble floor, and no evidence of extension of the subepithelial separation at the periphery of the lesion. For the other variants, only the presence or absence was considered.

The data were tabulated and analyzed using the IBM SPSS Statistics software version 24.0 (IBM Corporation, New York, United States). Descriptive statistical analysis was obtained for all variables described, being presented in absolute and relative numbers.

Results

Clinical findings

Among 6,875 lesions diagnosed at the Oral Pathology Laboratory, from 2000 to 2019, 401 (5.8%) were oral mucocoeles. Most oral mucocoeles (235; 58.6%) occurred in women and 166 (41.4%) in men, with a mean age of 21 years (ranging from 4 months to 75 years).

The lower lip was the most common affected site, with 317 lesions (79.1%), followed by ventral surface of tongue (24; 6.0%), buccal mucosa (20; 5.0%), and floor of the mouth (19; 4.7%). The other sites are described in Table 1. The mean time of complaint was six months, ranging from three days to 20 years. Twenty-four patients (6.0%) reported periods of remission and relapse. The type of complaint referred by the patients was available in 158 cases (39.4%). All lesions were asymptomatic, only one patient reported pain because of the habit of nibbling the affected region.

Table 1. Clinical diagnosis versus anatomical location of oral mucocoeles.

Clinical diagnosis	Location							Total (%)
	Lower lip	Tongue (ventral surface)	Buccal mucosa	Floor of the mouth	Palate	Tongue (border)	Not reported	
Mucocoele	274	15	13	05	02	02	-	311 (77.6)
Fibrous hyperplasia	19	05	05	-	-	01	-	30 (7.5)
Ranula	-	-	-	01		-	-	1 (0.25)
Pyogenic granuloma	04	02	-	-	-	-	-	6 (1.5)
Pleomorphic adenoma	-	-	-	13	-	-	-	13 (3.2)
Papilloma	03	-	-	-	02	-	-	5 (1.2)
Mucous retention cyst	-	-	-	-	01	-	-	1 (0.25)
Adenocarcinoma	01	-	-	-	-	-	-	1 (0.25)
Fibroepithelial polyp	01	-	-	-	-	-	-	1 (0.25)
Leukoplakia	01	01	-	-	-	-	-	2 (0.5)
Lipoma	01	-	-	-	-	-	-	1 (0.25)
Congenital epulis	-	-	01	-	01	-	-	2 (0.5)
Verruciform xanthoma	01	-	-	-	-	01	-	2 (0.5)
Not reported	12	01	01	-	-	-	11	25 (6.25)
Total (%)	317 (79.1)	24 (6.0)	20 (5.0)	19 (4.7)	6 (1.5)	4 (1.0)	11 (2.7)	401

Clinical aspects were partially reported in 337 (84%) cases. The characteristics described were color – translucent (n = 27; 6.6%), bluish (n = 23; 5.7%), normal mucosa (n = 119; 29.7%), yellow (n = 3; 0.7%), red (n = 14; 3.5%), whitish (n = 29; 7.2%) or brown (n = 5; 1.2%); format – nodular (n = 177; 42.9%), vesicular (n = 27; 6.7%), bullous (n = 9; 6.0%), papular (n = 14; 3.5%); episodes of remission and relapse (n = 24; 6.0%); and consistency as softened (n = 86; 21.4%), firm (n = 21; 5.2%) fibrous (n = 6; 1.5%), fibroelastic (n = 4; 0.9%) or elastic (n = 1; 0.2%). The mean size was 8.9 mm, ranging from 1.0 mm to 50 mm. Regarding clinical diagnostic hypotheses, mucocoele was the main suggestion (n = 311; 77.5%) (Table 1). However, in 13 lesions (3.2%) located in floor of the mouth, pleomorphic adenoma was the clinical diagnosis (Table 1). Most lesions were excised (273; 68.1%) and 37 (9.2%) were submitted to incisional biopsy. This information was not available in 25 lesions (6.2%).

Microscopical findings

The overlying oral mucosa was normal and intact in 200 patients (49.8%) (Fig. 1), while in 152 (38%) there was epithelial atrophy, 25 of their in the superficial variant. In 45 lesions (11.2%) the epithelium was absent. In addition, ulceration was observed in three patients (0.8%), and in only one (0.2%) there was epithelial hyperplasia. Myxoid mucus was predominant, corresponding to 225 lesions (56.1%). Only 40 (9.8%) had hyaline mucus (Fig. 1) and 134 (33.4%) had both myxoid and hyaline mucus simultaneously.

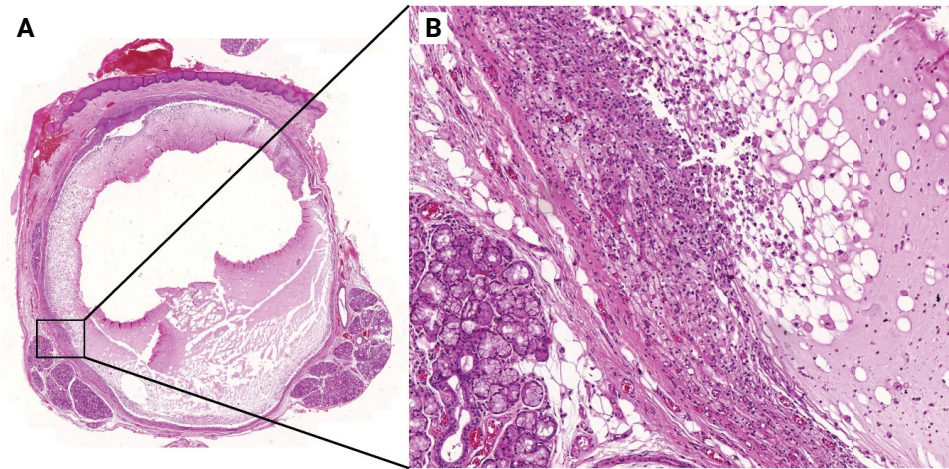


Figure 1. Classical histological finding in an oral mucocoele. (A) Cavity filled with mucus, which appears as a homogeneous, hyaline, and eosinophilic. Normal minor salivary glands were associated with the lesion. In addition, in the surface, squamous epithelium from the oral mucosa is also observed (HE, 10x). (B) The cavity is lined by granulation tissue with numerous macrophages. Several macrophages are also observed immersed in the extravasated mucus (HE, 200x).

Eighty-three (20.8%) uncommon histological variants were identified and illustrated in detail Fig. 2. Of these, the superficial mucocoeles was the most frequent variant (n=25; 6.2%), while the clear cells change occurred in two lesions (0.5%) (Fig. 2). Myxoglobulosis was found in 10 (2.5%) lesions, mainly in lower lip. The data on uncommon histological variants described are in Table 2.

Table 2. Anatomical location of mucocoeles versus unusual histopathological features.

Anatomical location of mucocoeles	Unusual histopathological features						Total
	Superficial mucocoeles	Significant reduction in the cavity lumen	Dissociation of collagen fibers after mucin extravasation	Myxoglobulosis	Papillary synovial metaplasia-like changes	Clear cell change	
Lower Lip	20	18	12	08	08	01	67
Tongue (ventral surface)	04	03	01	01	-	-	09

Continue

Continuation							
Buccal mucosa	01	01	01	-	01	01	05
Floor of the mouth	-	-	-	-	-	-	-
Palate	-	-	01	-	-	-	01
Tongue (border)	-	-	-	01	-	-	01
Not reported	-	-	-	-	-	-	-
Total	25	22	15	10	09	02	83

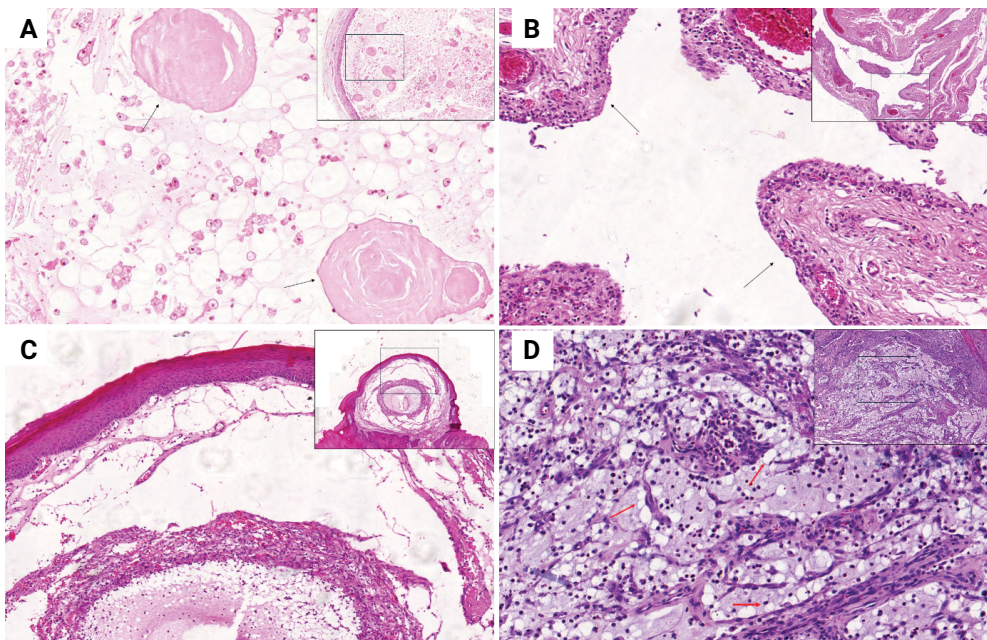


Figure 2. Unusual histopathological features in oral mucocoeles. (A) Myxoglobulosis, characterized by hyalinized globular structures in the lumen. *black arrow* (HE, 100x and 200x). (B) Papillary synovial metaplasia showing synovial membrane-like structures resembling joint spaces. *black arrow* (HE, 100x and 200x). (C) Superficial mucocoele presenting as mucus adjacent to the surface epithelium (HE, 50x, and 100x). (D) Dissociation of collagen fibers after mucin extravasation driving a late host response mediated by macrophages. *red arrow* (hematoxylin and eosin, 100x and 200x).

In connective tissue, the most common finding was the presence of chronic inflammatory reaction, observed in 399 lesions (99.5%), followed by vascular congestion in 255 (56.1%). The minor salivary glands were present in 299 specimens (74.6%), all mucous. In 102 cases (25.4%), the minor salivary glands were absent, with 80 lesions (78.4%) located in the lower lip. The glandular ducts present in the tissue samples showed rupture in 11 patients (2.7%) and were dilated in 51 (12.7%). In 17 patients (4.2%), the ducts were simultaneously dilated and ruptured.

Discussion

Oral mucocoeles are common^{1,9}. In previous studies, these lesions accounted for 4.61% to 5.8% of all oral biopsies^{1,2,12,14}, similar to present series. The prevalence among genders is quite variable^{1,8,11,12}. In the present study, there was a slight predilection for females, as found in some surveys⁶. However, other series have found higher frequency in male individuals^{2,13}. Oral mucocoeles are more frequent in young adults, between the second and third decades of life, as they are more prone to traumas that induce mucin leakage. Despite of this, oral mucocoeles can occur in any age group, from babies to the elderly^{7,16,19}, as observed in this series.

The clinical features of the lesion depend on its depth in the mucosa, size, vascularization, and elasticity of the overlying epithelium^{5,10}. Those located more superficially appear as vesicles or blisters with a bluish color, whereas those that are deeper in the mucosa have a nodular appearance and tend to have normal mucosa color¹. The lower lip is the most common affected site, followed by the ventral surface of the tongue, as also observed in this survey. These sites are more susceptible to traumas, especially in the regions of the dental cusps^{1,5,7,8,13}. Although trauma is considered the determining etiologic factor for oral mucocoeles, in the present study, only 17 lesions (4.2%) presented this report. Often, the data collected during anamnesis are insufficient to prove this causal association. This is possibly the result of missing information in the patient's record or the occurrence of an imperceptible or irrelevant trauma by the patient.

In this series, mucocoele was the most frequent clinical diagnosis, resulting in excisional biopsy in most patients (68.1%). Similarly, Bezerra et al.¹ (2016) showed correlation between the clinical and histopathological diagnoses in 78.4% of the cases, resulting in the same treatment choice. However, other lesions were considered in the clinical differential diagnosis. Although mucocoeles rarely represent a challenge for clinical diagnosis, pleomorphic adenoma was the main clinical diagnosis in 13 lesions located in the floor of the mouth. In this location, deeper mucous extravasation phenomenon may present as a tumor-like lesion colored as normal mucosa, which may explain the misleading suggestion of pleomorphic adenoma as clinical hypothesis.

Treatment of mucocoeles consists in surgical excision, making sure to include the associated salivary glands, as well as all glands present in the adjacent area to the lesion, because of the risk of recurrence^{4,5,19}. However, small and superficial lesions can resolve spontaneously without leaving sequela¹⁹. If no treatment is performed, episodes of decrease and increase in size can be noticed, owing the rupture of the lesion and subsequent production and accumulation of mucus²⁰. In this study, no salivary glands were observed in 25.4% of the specimens, most of them were in the lower lip. This can result in recurrence episodes.

Histologically, mucocoeles appeared as a mucus-filled cavity, surrounded by granulation tissue and no epithelial lining¹². Many macrophages are found immersed in the extravasated mucus, especially of the xanthomatous type^{21,22}. Although most mucocoeles did not represent a diagnostic challenge, they may have some unusual histopathological characteristics that may represent difficulties in the diagno-

sis^{9,12-14,17-22}. Papillary synovial metaplasia-like changes are characterized by the proliferation of structures similar to synovial membranes present in joint spaces. Most of them have been related particularly to sliding trauma²³. However, its occurrence in oral mucocoeles is rare, which suggests that the dynamics of traumatic stimuli may be an important determinant in their development¹². The membrane of this variant may show microscopic changes during the development of the mucocoeles. Immature lesions exhibit an intense and disorganized cellular arrangement. Mature lesions show a reduction in the number of cells, but present a greater organization and smooth surface, while long-lasting lesions display well-developed hyalinization, and a marked decrease in cellularity²³. The presence of this histological variant is variable, ranging from 0%¹³ to 8%¹⁴ of previous studied samples. In the present study, nine (2.2%) oral mucocoeles presented papillary synovial metaplasia-like changes. It is important that the pathologist aware how to identify this variant to avoid misdiagnosis. Warthin's tumor should be considered as a differential diagnosis in cases of mucocoeles with synovial metaplasia, because of the cystic papillary growth and eosinophilic surface. However, there are characteristics that contribute to distinguish these lesions, such as the lower lip being the preferred location of mucocoeles, in contrast to Warthin's tumor that rarely occur outside parotid glands. In addition, Warthin's tumor presents many oncocyctic cells with eosinophilic cytoplasm¹⁵.

Another variant analyzed was the separation of collagen fibers after extravasation, being observed in 3.7% of the sample. This alteration occurs during the development of myxoglobulosis⁹. In a previous study, 4.49% of the cases presented the dissociation of collagen fibers¹⁴. Myxoglobulosis consists of a globular structure, not surrounded by epithelium and containing eosinophilic, lamellar, and amorphous or fibrillar material⁹. For Shah⁹ (2003), this structure has a development pattern consistent with the traumatic origin of the mucocoeles. At the initial stage, there is mucin extravasation that drives a host response, initially mediated by neutrophils, followed later by macrophages. This extrusion of material in the connective tissue causes the separation of collagen fibers, which are surrounded by macrophages and acquire a globular appearance. Despite this, its etiology and pathogenesis are still uncertain^{13,14}. While in this study myxoglobulosis were present in 10 lesions (2.5%), the literature reports a prevalence that varies from 0.4% to 31%^{9,12-14}. This highly variable prevalence may be casual or indicates differences in the definition of this histological variant. It is worth mentioning that this variant has no clinical significance. This can be seen by the absence of clinical and prognostic differences between mucocoeles associated with myxoglobulosis when compared to traditional cases¹⁶.

Significant reduction in the lumen may occur because of the presence of large papillae in the granulation tissue that protrude into the cavity^{12,15}. This variant was the second most common change (5.7%), similar to found in other series¹⁴. Superficial mucocoeles are characterized by the leakage of mucus at the interface of the connective-epithelial tissue and can be solitary or multiple¹⁷. This variant was initially described by Eveson¹⁷ (1988) and may be associated with other diseases, such as pemphigoid, bullous lichen planus, herpetic lesion, venous lake, and graft-ver-

sus-host disease^{1,12,16-18}. Radiation-induced superficial mucocoeles have been also described²⁴. In this study, this variant was the most prevalent, being observed in 6.2% of the sample.

The clear cells change variant was observed in 0.5% of the cases. It is characterized by atypical arrangement of macrophages, which are quite numerous and bulky, and can fill the entire lumen or involve the entire cavity¹⁴. This change is usually the result of intracellular storage of glycogen, mucin or lipid, fixation artifacts or due to the scarcity of organelles²². In these cases, clear cells neoplasms should be considered in the histopathological differential diagnosis. Several salivary gland tumors may present clear cells, comprising a diverse group of benign and malignant lesions with varying clinical and pathological characteristics. Among them, pleomorphic adenoma, myoepithelioma, clear cell oncocytoma, mucoepidermoid carcinoma, and acinar cell carcinoma should be included²⁵. In some cases, immunohistochemical reactions are necessary to characterize the origin of clear cells, macrophagic (confirming the diagnosis of mucocoele) or epithelial.

Myxoid-type mucus was predominant in this sample, corresponding to 225 lesions (56.1%), and 134 (33.4%) had both myxoid and hyaline mucus. However, other series revealed a predominance of mucus in a fibrillar aspect, with no presence of myxoid mucus or both⁸. This variation may be result from several factors, such as duration of mucus accumulation, exposure during macroscopy, histological technical processing, and uneven distribution of mucus in the cavity due to perforations, clamps, and incisions.

In conclusion, although the diagnosis of oral mucocoeles is not a challenge, this study highlights that unusual histological variants may mimic other benign and malignant salivary glands lesions. Furthermore, all excised tissue should be submitted to histopathological analysis to confirm the diagnosis, even in cases of common clinical presentations.

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Data availability

The authors confirm that data supporting the findings of this study are available within the article. Raw data that support the findings of this study are available from the corresponding author, upon request.

Author Contribution

Ângela Nathalie Silva Lima: Investigation; Data Curation; Formal analysis; Visualization; Writing - Original Draft. **Augusto César Leal da Silva Leonel:** Investigation. Writing - Original Draft; Formal analysis. **Hélen Kaline Farias Bezerra:** Investigation; Writing - Original Draft. **Jurema Freire Lisboa de Castro:** Formal analysis; Writing - Review & Editing; Supervision. **Elaine Judite de Amorim Carvalho:**

Formal analysis ; Writing - Review & Editing; Supervision. **Danyel Elias da Cruz Perez:** Conceptualization; Methodology; Writing - Review & Editing; Supervision. All authors actively revised and approved the final version of the manuscript.

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