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**LETTER TO EDITOR** **TRANSLATIONAL AND CLINICAL RESEARCH**

Fabrizio Cialente, et al.: Differential diagnosis of lingual cysts

# Lingual cyst with respiratory epithelium: The importance of differential diagnosis

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**To the Editor:**

Lingual cyst with respiratory epithelium (LCRE) is a very rare congenital cyst of the tongue, floor of the mouth, pharynx or hypopharynx with 21 cases reported in the literature (1, 2).

Differential diagnosis is very important for patients presenting with lingual cysts, as this may impact treatment and follow-up. LCRE should be included in the different diagnosis of dermoid cyst (3), teratoid cyst (4), epidermoid cyst (5), thyroglossal duct cyst (6), lymphoepithelial cyst (7), mucocele or ranula (8). Each entity has a peculiar histologic presentation, although the clinical aspect may be very similar (1). The dermoid cyst is lined by a keratinized squamous epithelium and contains skin appendages in the cyst. Epidermoid cyst is similar to the dermoid cyst but is characterized by non-keratinized squamous epithelium and has a lumen filled of keratin. Teratoid cyst contains derivatives of the endoderm, ectoderm and/or mesoderm. The thyroglossal duct cyst is usually lined by columnar, stratified squamous epithelium, or an intermediate transition type of epithelium, with the mandatory presence of thyroid tissue in the cyst wall. Lymphoepithelial cyst is identified by the presence of the lymphoid aggregates in the cyst wall. A mucous retention cyst, so called mucocele or ranula, contains mucin and granulation tissue (1).

In order to differentiate LCRE from other types of developmental cysts, Manor et al. (9) recommended the use of histologic descriptive terminology. According to that classification scheme, the epithelial lining of the LCRE is composed predominantly by respiratory tract epithelium-pseudostratified ciliated cuboidal and columnar, differentiating it from the most commonly observed lingual alimentary cyst, mainly lined by gastric or intestinal mucosae. However, many reports in the literature described the epithelial lining of the lingual cyst as composed of both types by epithelium (9).

The pathogenesis of the LCRE is unknown, but it most likely represents a congenital abnormality arises from a misplacement of undifferentiated cells of the ventral portion of the foregut in week 4 of embryonic development (1, 9). In the third week of embryonic development, the foregut divides into a ventral part, containing components of the endoderm that lead to the development of the

laryngo-tracheo-bronchopulmonary tree, and a dorsal part that becomes the proximal gastrointestinal tract. During this time of differentiation, embryonal rests may be misplaced and entrapped in the pharyngeal arches (which contains the developing tongue), due to their proximity with the primitive foregut. These entrapped rests, which are pluripotential, can differentiate into respiratory epithelium and form a lingual cyst (10).

We have recently treated a case of a 44-year-old male with a palpable, soft, tender mass occupying the entire width of the tongue, causing a mild restriction of tongue movement and elevation of anterior floor of the mouth. Magnetic resonance imaging (MRI) showed a heterogeneously hyperintense cystic mass measuring 6x6x4cm in size, located in the sublingual space (Figure 1). Histologic examination of the surgical specimen revealed a cystic lesion lined by well-differentiated ciliated, pseudo-stratified, columnar epithelium (Figure 2A and 2B). Immunohistochemical analysis, performed as described previously (10, 11), revealed the respiratory-type origin of the epithelial cell lining. Indeed, epithelial lining cells were immunoreactive for CK7 and TTF1 but not for CK20 and Thyroglobulin (Figure 2C-E). In addition, a thick smooth muscle Desmin-positive layer (Figure 2A and 2F) was present underneath the epithelial lining. Based on these findings, the lesion was classified in the spectrum of the oral foregut duplication cysts. More specifically, the respiratory type of the epithelial lining and the site of the lesion were *per se* consistent with the diagnosis of LCRE (9).

To date, 21 cases of LCRE have been reported in the literature (1). Several case reports that were considered in previous reviews as LCRE were excluded because not lined with Manor's histological criteria. According to that, only 7 (cases 4,6,7,9,11,12, and 15) of the 16 cases reported by Wiersma et al. (12) and one case in the series of 16 reported by Chai et al. (4) were included in this review (Supplemental Table 1). The age of presentation ranged from 6 months to 42 years of age, with a slight male predilection. Except for five adult case, all cysts have occurred in the pediatric age. Clinically, the lingual cyst appears on the dorsal tongue, or the floor of the mouth; a common sign is the swelling of the tongue which causes difficulty in eating, drinking, speaking and breathing. All

patients were treated by completely excision of the cyst or the swelling marsupialization. No recurrence was reported (1).

In conclusion, various well-established types of developmental cyst have been described in the tongue. LCRE represents a distinct entity histologically characterized by the presence of respiratory tract epithelium, pseudostratified ciliated columnar and cuboidal, with the absence of any other structures within the cyst wall. These characteristics should be always considered as, because of its rarity, LCRE is often overlooked with consequences on treatment and prognosis of affected patients.

**KEYWORDS**: Lingual cyst with respiratory epithelium; differential diagnosis; tongue; lingual cysts

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**FIGURES**

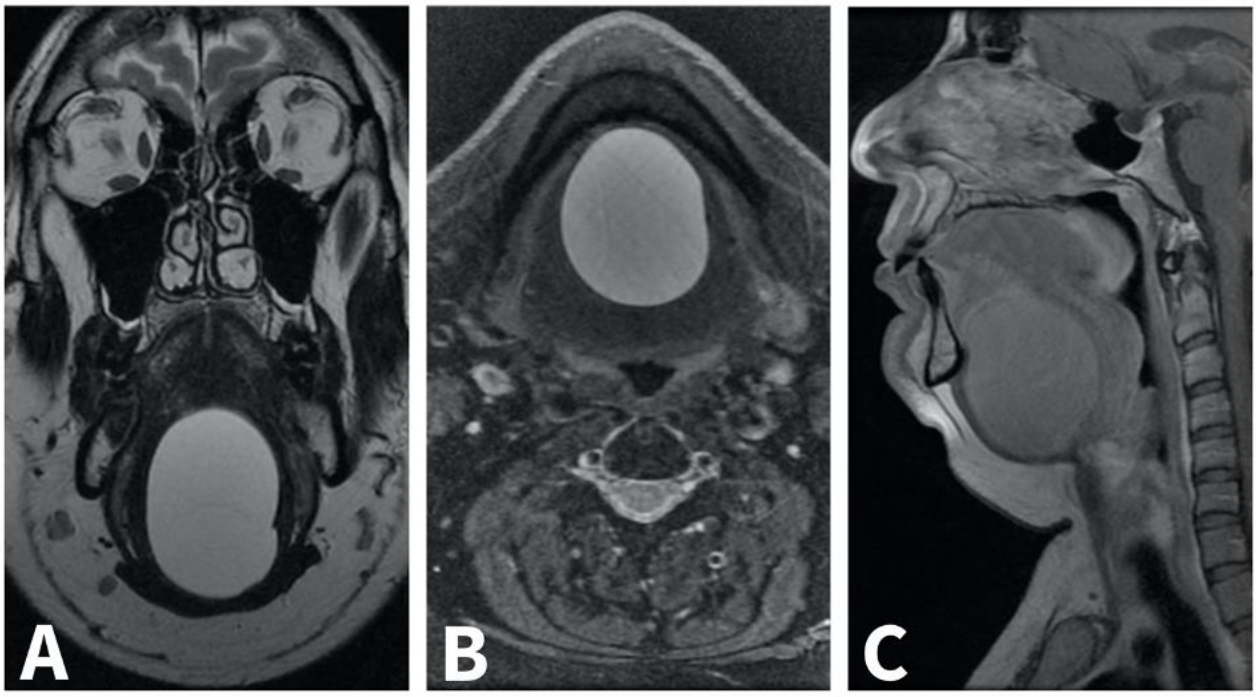


**FIGURE 1.** Magnetic resonance imaging (MRI) of a patient with LCRE that demonstrates an approximately 6 cm cystic mass beneath the tongue in the (**A**) coronal, (**B**) axial and (**C**) sagittal planes. The lesion shows high signal on both basic (**A**) and fat-saturated T2 weighted images (**B**), no contrast enhancement on T1 sequences (**C**). These aspects are in keeping with simple fluid collection. (**A)** COR T2 FSE; (**B)** AX FRFSE T2 Fat Sat; (**C)** SAG T1 FSE + contrast.

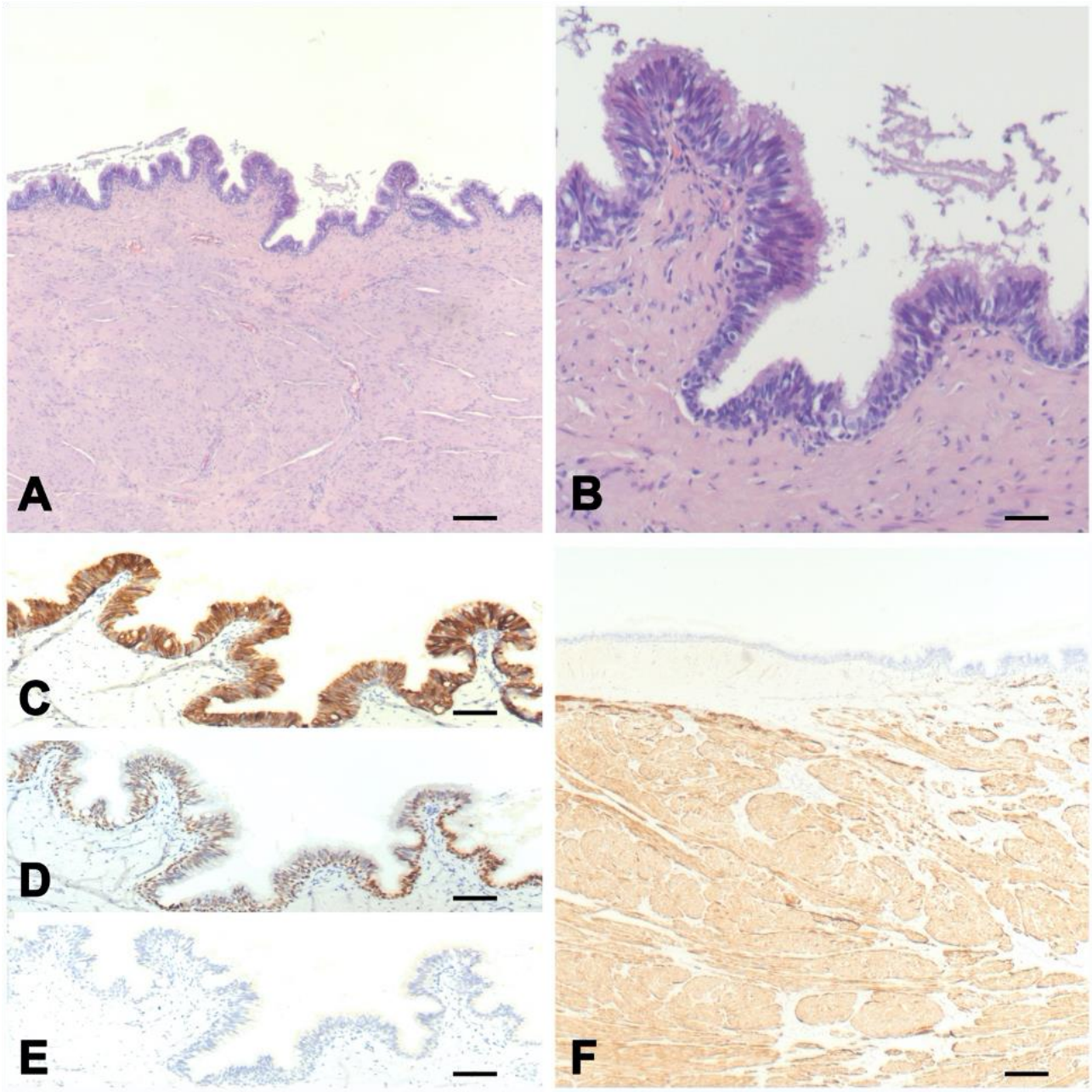


**FIGURE 2.** LCRE: Low-power magnification of the cyst wall is illustrated in **A**. The epithelial layer consists of ciliated, pseudo-stratified, columnar cells (**B**) which are immunoreactive for CK7 (**C**) and TTF1 (**D**) but not for Thyroglobulin (**E**). The thick smooth muscle cell layer underneath the epithelial lining (**A**) is highlighted by Desmin immunostaining (**F**). **A** and **B**: hematoxylin and eosin. Bars: 200 μm in **A** and **F**; 100 μm in **B**; 80 μm in **C**, **D** and **E**.

SUPPLEMENTAL DATA

## TABLE S1.

| | *Author (Year)* | *No. of cases* | *Age/ Sex* | *Site* | *Clinical Symptoms* | *Histopathologic Features (cyst lining)* | *Treatment Done* | *Follow-up* |
|---|---|---|---|---|---|---|---|---|
| 1. | Fink (1963) (13) | 1 | 5/M | Dorsum tongue, anterior third | Painless swelling, but difficulty eating and drinking | Lined in different parts by pseudostratified ciliated columnar epithelium and by cuboidal epithelium. The fibrous capsule showed moderate inflammation of chronic inflammatory cells | Enucleation | Recurrence after 2 years |
| 2. | Constantinides et al. (1982) (14) | 1 | 9 month old/F | Anterior, ventrum of tounge | Since birth, difficulty in eating, inability in closing mouth | Lined by stratified squamous epithelium and ciliated and nonciliated cuboidal "respiratory type" epithelium | NA | NA |
| 3. | Wiersma et al. (1992) (12) | 7 | Various | Anterior two-thirds of tounge in all patients | Various | Lined by respiratory epithelium in all the cysts with other areas of squamous, cuboidal or columnar epithelium | Sagittal glossal split was preformed, allowing complete excision of the cyst | NA |
| 4. | Shear M. (1992) (15) | 1 | 2/F | NA | Since birth | Lined in different parts by pseudostratified ciliated columnar epithelium and by cuboidal epithelium. The fibrous capsule showed moderate inflammation of chronic inflammatory cells | NA | NA |
| 5. | Naidoo LC (1997) (16) | 1 | 42/M | Center of dorsum of tongue | Swelling present since 6 months, minor discomfort on eating and speaking | Plaques of stratified squamous epithelium and areas of pseudostratified, nonciliated cuboidal and ciliated columnar epithelium resting on a bland connective tissue | Sagittal glossal split was performed and the lesion was enucleated | No recurrence over a period of 4 years |

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| 6. | Kim et al. (1998) (17) | 1 | 27/M | Sublingual, hard swelling | No specific symptoms | Lined by pseudostratified columnar epithelium with focal squamous metaplasia and goblet cells<br>Calcium deposit noted | NA | NA |
| 7. | Manor et al. (1999) (9) | 1 | 11/M | Body of tongue | Macroglossia, difficulty with speech and swallowing, night vomiting, mild restriction of tongue movement | Lined by pseudostratified ciliated columnar epithelium with goblet cells and cuboidal epithelium | NA | NA |
| 8. | Ameh EA & Mshelbwala P (2002) (18) | 1 | 20 month old/F | NA | Since birth, interfered with breathing | Epithelial lining of stratified squamous and respiratory type epithelium | NA | No recurrence |
| 9. | Erdogan et al. (2005) (19) | 1 | 9/M | NA | NA | Lingual cyst of foregut origin lined by respiratory epithelium. | NA | NA |
| 10. | Azanero et al. (2009) (20) | 2 | 4/M<br><br>21/M | Right ventral tongue<br><br>Anterior middle third of dorsum of tongue | Blue swelling present since birth, difficulty in breast feeding<br><br>Since 19 years, asymptomatic, gradually increasing in size, difficulty in eating and talking | Lined predominantly by ciliated pseudostratified columnar respiratory epithelium, and foci of squamous epithelium. The capsule was formed by a thick, uniform, edematous connective tissue stroma, infiltrated by mild mononuclear inflammatory infiltrates. Focal areas of PAS and Mucicarmine stain positivity<br><br>Lined by ciliated pseudostratified columnar respiratory epithelium, and focal areas of squamous epithelium. The cyst wall was composed of fibrous connective tissue. Focal areas of PAS and Mucicarmine stain positivity | Marsupialisation was performed, after which the lesion persisted and a definitive surgical removal was performed<br><br>Well encapsulated cyst was removed under general anaesthesia | No recurrence after 3 years of follow up<br><br>No recurrence after 2 years of follow up |
| 11. | Boffano et al. (2009) (21) | 1 | 35/F | Floor of mouth | Asymptomatic | Lined by pseudostratified, ciliated columnar epithe- lium with goblet cells with chronic inflammation in the wall | NA | NA |
| 12. | Chai et al. (2011) (4) | 1 | 6 month old/F | Ventral tongue | Feeding difficulties | Lined by pseudostratified, ciliated respiratory-type epithelium | NA | NA |

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|---|---|---|---|---|---|---|---|---|
| 13. | Juneja et al. (2011) (3) | 1 | 1/F | Anterior dorsal tongue (right) | 3×3 cms swelling on the right side of the tongue, present since birth, difficulty in eating | Lined by pseudostratified ciliated columnar epithelium in majority of areas with few areas showing non keratinized stratified squamous epithelium | Marsupialisation | No recurrence |
| 14. | Fortier et al. (2013) (22) | 1 | 17 month old/F | Left anterior tongue | Asymptomatic | Lined by pseudostratified respiratory epithelium with ciliated cells Inflammation in cyst wall, some mucinous glands | NA | NA |
| 15. | Kwak et al. (2014) (23) | 1 | 2/F | Ventral tongue | Asymptomatic | Lined by pseudostratified, ciliated columnar epithe- lium considered to be respiratory epithelium | NA | NA |
| 16. | Peters et al. (2018) (13) | 2 | 10/M<br><br>27/F | Floor of mouth<br><br>Floor of mouth | Asymptomatic<br><br>Asymptomatic | Lined by ciliated columnar epithelium<br>Lined by pseudostratified columnar epithelium with globet cells | Excision under cover of general anaesthesia | No recurrence |
| 17. | Our case | 1 | 44/M | Anterior two-thirds of tounge(sublingual space) | 6x6x4 cm; present since 9 months; swelling on the body of tongue; macroglossia and difficulties in speech and swallowing | Lined by well-differentiated ciliated, pseudostratified, columnar epithelium; in addition, a thick smooth muscle Desmin-positive layer was present underneath the epithelial lining | Excision under cover of general anaesthesia | Under follow-up |
| | NA - Description not available | | | | | | | |