Lingual cyst with respiratory epithelium: The importance of differential diagnosis

Fabrizio Cialente[1], Giulia De Soccio[1], Vincenzo Savastano[2], Michele Grasso[1], Michele Dello Spedale Venti[3], Massimo Ralli[1], Mara Riminucci[3], Marco de Vincentiis[4], Alessandro Corsi[3], Antonio Minni[1]*

The 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. The LCRE should be included in the different diagnosis of a dermoid cyst [3], teratoid cyst [4], epidermoid cyst [5], thyroglossal duct cyst [6], lymphoepithelial cyst [7], and 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. The epidermoid cyst is similar to the dermoid cyst but is characterized by non-keratinized squamous epithelium and has a lumen filled with keratin. The 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. The lymphoepithelial cyst is identified by the presence of 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 the 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 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 of epithelium [9].

The pathogenesis of LCRE is unknown, but it most likely represents a congenital abnormality that arises from a misplacement of undifferentiated cells of the ventral portion of the foregut in week 4 of embryonic development [1,9]. In the 3rd 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 the anterior floor of the mouth. Magnetic resonance imaging (MRI) showed a heterogeneously hyperintense cystic mass measuring 6 × 6 × 4 cm in size, located in the sublingual space (Figure 1). Histologic examination of the surgical specimen revealed a cystic lesion lined by well-differentiated ciliated, pseudostratified, columnar epithelium (Figure 2A and B). Immunohistochemical analysis, performed as described previously [10,11], revealed the respiratory-type origin of the epithelial cell lining. Indeed, the epithelial lining cells were immunoreactive for cytokeratin 7 (CK7) and thyroid transcription factor 1 but not for CK20 and thyroglobulin (Figure 2C-E). In addition, a thick smooth muscle desmin-positive layer (Figure 2A and F) 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 the previous reviews as LCRE were excluded because not lined with the Manor's histological criteria. According to that, only

[1]Department of Sense Organs, University Sapienza of Rome, Rome, Italy
[2]UOSD Pediatric ENT, DAI Head-Neck, University Hospital Policlinico Umberto I, Rome, Italy
[3]Department of Molecular Medicine, University Sapienza of Rome, Rome, Italy
[4]Department of Oral and Maxillo-Facial Surgery, University Sapienza of Rome, Rome, Italy

*Corresponding author: Antonio Minni, Department of Sense Organs, University Sapienza of Rome, Viale dell'Università 33, 00168 Rome, Italy. E-mail: antonio.minni@uniroma1.it

DOI: https://dx.doi.org/10.17305/bjbms.2020.4716

Submitted: 28 March 2020/Accepted: 20 May 2020

Conflict of interest statement: The authors declare no conflict of interests

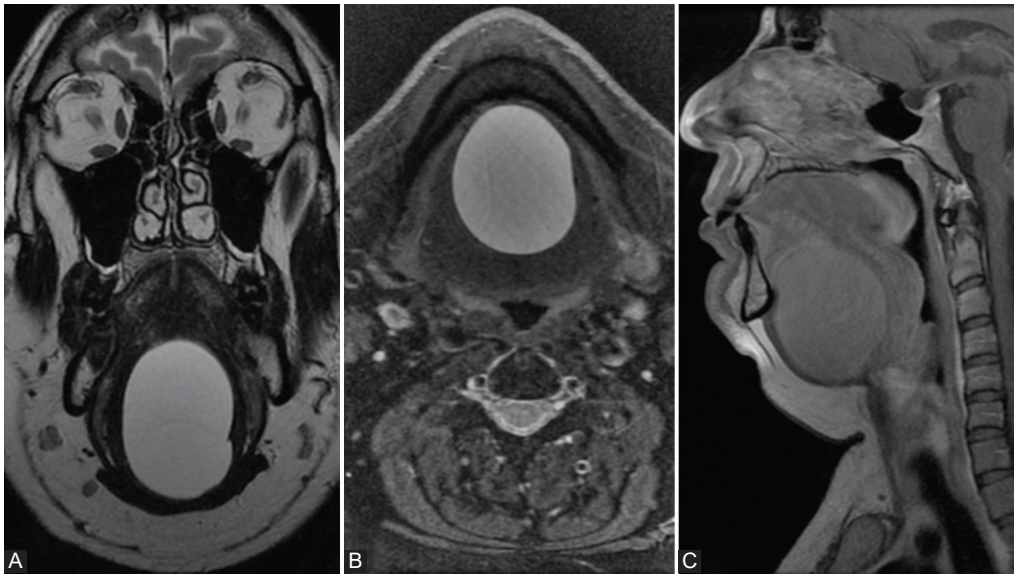

FIGURE 1. Magnetic resonance imaging of a patient with a lingual cyst with respiratory epithelium (LCRE) that demonstrates an approximately 6 cm cystic mass beneath the tongue in the coronal (A), axial (B), and sagittal planes (C). The lesion shows high signal on both basic (A) and fat-saturated T2-weighted (B) images, 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.

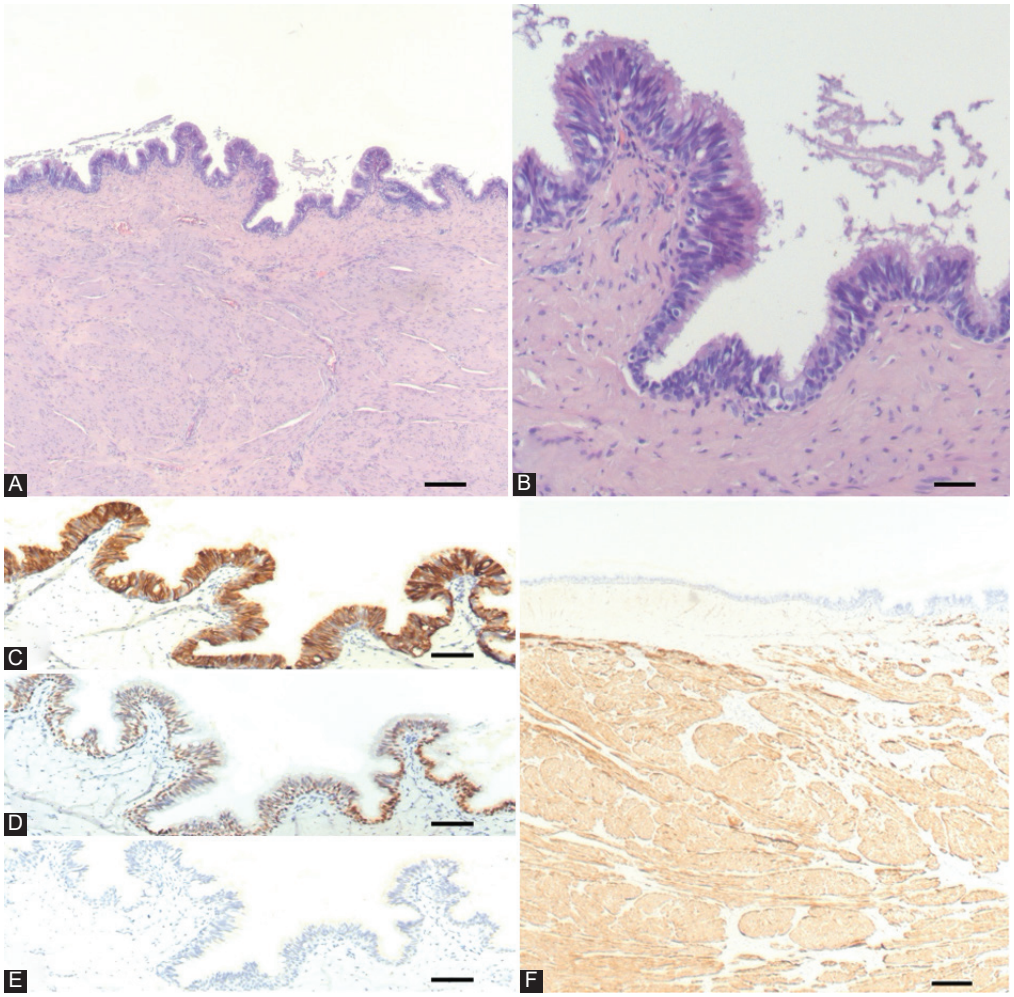

FIGURE 2. Lingual cyst with respiratory epithelium (LCRE): low-power magnification of the cyst wall is illustrated in (A). The epithelial layer consists of ciliated, pseudostratified, columnar cells (B) which are immunoreactive for cytokeratin 7 (C) and thyroid transcription factor 1 (D) but not for 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.

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 (Table S1). The age of presentation ranged from 6 months to 42 years of age, with a slight male predilection. Except for 5 adult cases, all cysts 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 complete excision of the cyst or the swelling marsupialization. No recurrence was reported [1].

In conclusion, various well-established types of developmental cysts have been described in the tongue. The 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 always be considered as, due to its rarity, the LCRE is often overlooked with consequences on the treatment and prognosis of affected patients.

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

REFERENCES

[1] Peters SM, Park M, Perrino MA, Cohen MD. Lingual cyst with respiratory epithelium: Report of 2 cases and review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol 2018;126(6):e279-e84. https://doi.org/10.1016/j.0000.2018.05.011.

[2] Awouters P, Reychler H. Enteric duplication in the oral cavity. Int J Oral Maxillofac Surg 1991;20(1):12-4. https://doi.org/10.1016/s0901-5027(05)80687-3.

[3] Juneja M, Boaz K, Srikant N, Nandita KP, Vidya M. Lingual cyst lined by respiratory epithelium: A case report and review of literature. Fetal Pediatr Pathol 2011;30(4):225-32. https://doi.org/10.3109/15513815.2011.555807.

[4] Chai RL, Ozolek JA, Branstetter BF, Mehta DK, Simons JP. Congenital choristomas of the oral cavity in children. Laryngoscope 2011;121(10):2100-6. https://doi.org/10.1002/lary.21758.

[5] Milam M, Hill SA, Manaligod JM. Lingual dermoid cysts. Otolaryngol Head Neck Surg 2003;128(3):428-9. https://doi.org/10.1067/mhn.2003.15.

[6] Shen J, Chen XM, Wang SZ, Wang L, Xiong SC. Clinicopathological and immunohistochemical study of oral teratoid cyst. Zhonghua Kou Qiang Yi Xue Za Zhi 2005;40(1):62-6.

[7] Correa MS, Fonoff Rde N, Ruschel HC, Parizotto SP, Correa FN. Lingual epidermoid cyst: Case report in an infant. Pediatr Dent 2003;25(6):591-3.

[8] Guerin N, Urtasun A, Chauveau E, Julien M, Lebreton M, Dumon M. Lingual thyroid and intra-lingual thyroglossal cyst. Apropos of 2 cases. Rev Laryngol Otol Rhinol (Bord) 1997;118(3):183-8.

[9] Manor Y, Buchner A, Peleg M, Taicher S. Lingual cyst with respiratory epithelium: An entity of debatable histogenesis. J Oral Maxillofac Surg 1999;57(2):124-7; discussion 8-9. https://doi.org/10.1016/s0278-2391(99)90222-7.

[10] Corsi A, Ciofalo A, Leonardi M, Zambetti G, Bosman C. Recurrent inflammatory myofibroblastic tumor of the glottis mimicking malignancy. Am J Otolaryngol 1997;18(2):121-6. https://doi.org/10.1016/s0196-0709(97)90100-9.

[11] Corsi A, Riminucci M, Petrozza V, Collins MT, Natale ME, Cancrini A, et al. Incidentally detected giant oncocytoma arising in retroperitoneal heterotopic adrenal tissue. Arch Pathol Lab Med 2002;126(9):1118-22. https://doi.org/10.1043/0003-9985(2002)126<1118:IDGOAI>2.0.CO;2.

[12] Wiersma R, Hadley GP, Bosenberg AT, Chrystal V. Intralingual cysts of foregut origin. J Pediatr Surg 1992;27(11):1404-6. https://doi.org/10.1016/0022-3468(92)90186-b.

[13] Fink HA. Retention cyst of the tongue (glossocele). Oral Surg Oral Med Oral Pathol 1963;16(11):1290-3. https://doi.org/10.1016/0030-4220(63)90401-8.

[14] Constantinides CG, Davies MR, Cywes S. Intralingual cysts of foregut origin. S Afr J Surg 1982;20(3):227-32.

[15] Altini M, Shear M. The lateral periodontal cyst: An update. J Oral Pathol Med 1992;21(6):245-50. https://doi.org/10.1111/j.1600-0714.1992.tb01004.x.

[16] Naidoo LC. Median lingual cyst: Review of the literature and report of a case. J Oral Maxillofac Surg 1997;55(2):172-5. https://doi.org/10.1016/s0278-2391(97)90238-x.

[17] Kim YS, Ahn SK, Lee SH. Sublingual foregut cyst. J Dermatol 1998;25(7):476-8. https://doi.org/10.1111/j.1346-8138.1998.tb02438.x

[18] Ameh EA, Mshelbwala P. Intralingual foregut duplication cyst: A case report. Niger Postgrad Med J 2002;9(1):32-3.

[19] Erdogan N, Dirim-Vidinli B, Uluc ME, Yigit S, Onal K. An unusual lingual cyst lined by respiratory epithelium. Kulak Burun Bogaz Ihtis Derg 2005;14(1-2):44-7.

[20] Azanero WD, Mazzonetto R, Leon JE, Vargas PA, Lopes MA, de Almeida OP. Lingual cyst with respiratory epithelium: A histopathological and immunohistochemical analysis of two cases. Int J Oral Maxillofac Surg 2009;38(4):388-92. https://doi.org/10.1016/j.ijom.2009.01.003.

[21] Boffano P, Zavattero E, Campisi P, Gallesio C. Surgical treatment of an oral cyst with respiratory epithelium. J Craniofac Surg 2009;20(4):1275-7. https://doi.org/10.1097/scs.0b013e3181ae1794.

[22] Fortier A, Boyer C, Ducasse H, Deville A, Chevallier A, Leroux C, et al. Bronchogenic cyst of the tongue in an infant. Rev Laryngol Otol Rhinol (Bord) 2013;134(3):157-9.

[23] Kwak EJ, Jung YS, Park HS, Jung HD. Oral foregut cyst in the ventral tongue: A case report. J Korean Assoc Oral Maxillofac Surg 2014;40(6):313-5. https://doi.org/10.5125/jkaoms.2014.40.6.313.

SUPPLEMENTAL DATA

TABLE S1. Cases of lingual cyst with respiratory epithelium reported in the literature

	Author (year)	Number 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 months old/F	Anterior, ventrum of tongue	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 tongue 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.	Altini and Shear (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 (1997) [16]	1	42/M	Center of dorsum of tongue	Swelling present for 6 months, minor discomfort when 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
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 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 and Mshelbwala (2002) [18]	1	20 months 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	Right ventral tongue	Blue swelling present since birth, difficulty in breastfeeding	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	Marsupialization was performed, after which the lesion persisted and a definitive surgical removal was performed	No recurrence after 3 years of follow-up
			21/M	Anterior middle third of dorsum of tongue	Since 19 years, asymptomatic, gradually increasing in size, difficulty in eating and talking	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	Well-encapsulated cyst was removed under general anesthesia	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 epithelium with goblet cells with chronic inflammation in the wall	NA	NA
12.	Chai et al. (2011) [4]	1	6 months old/F	Ventral tongue	Feeding difficulties	Lined by pseudostratified, ciliated respiratory-type epithelium	NA	NA

(*Contd...*)

TABLE S1. Cases of lingual cyst with respiratory epithelium reported in the literature (*Continued*)

	Author (year)	Number of cases	Age/sex	Site	Clinical symptoms	Histopathologic features (cyst lining)	Treatment done	Follow-up
13.	Juneja et al. (2011) [3]	1	1/F	Anterior dorsal tongue (right)	3×3 cm 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	Marsupialization	No recurrence
14.	Fortier et al. (2013) [22]	1	17 months 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 epithelium considered to be respiratory epithelium	NA	NA
16.	Peters et al. (2018) [1]	2	10/M 27/F	Floor of mouth Floor of mouth	Asymptomatic Asymptomatic	Lined by ciliated columnar epithelium Lined by pseudostratified columnar epithelium with goblet cells	Excision under cover of general anesthesia	No recurrence
17.	Our case	1	44/M	Anterior two-thirds of tongue (sublingual space)	6×6×4 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 anesthesia	Under follow-up

NA: Description not available.