Archives of Orofacial Sciences
The Journal of the School of Dental Sciences
Universiti Sains Malaysia

Arch Orofac Sci (2015), **10**(1): 34-40.

Original Article

Congenital epulis: immunohistochemical findings of 12 cases

Ajura Abdul Jalil *, Lukman Md Auzair, Lau Shin Hin

Stomatology Unit, Cancer Research Centre, Institute for Medical Research, 50588 Jalan Pahang, Kuala Lumpur, Malaysia.

* Corresponding author: ajura_jalil@yahoo.com

Submitted: 10/03/2015. Revised edition: 28/05/2015. Accepted: 09/06/2015. Published online: 09/06/2015.

Abstract Congenital epulis is a fairly rare soft tissue tumour occurring exclusively on the alveolar ridge of newborns. The exact origin of congenital epulis is still debatable. The objective of the study is to determine the clinicopathological features and immunohistochemical findings of congenital epulis. A retrospective study was carried out to determine the clinicopathological features of congenital epulis, diagnosed histologically in the main oral histopathology laboratory in Malaysia from 1967 to 2014. Immunostaining using vimentin, muscle specific actin, smooth muscle antigen, desmin, S100, CD34, CD68 and CD1a was carried out. Twelve cases of congenital epulis were reviewed. All of the patients were females and the presentation age ranged from 2 to 90 days. The patients comprised of 6 Malays, 3 Chinese, 2 Indians and 1 Orang Asli. Most of the cases (n=7) involved the maxillary ridge and presented as pedunculated well-defined lumps (n=8). Excisional biopsy was performed in all cases. Via immunohistochemistry, vimentin expression was observed in all cases; but negative for CD34, muscle specific actin, smooth muscle antigen, and desmin. CD1a and S100 positivity was seen in five cases. The interstitial cells were highlighted by CD68. Although congenital epulis has been first described 130 years ago, the exact nature of its histogenesis remains a mystery.

Keywords: alveolar ridge, congenital epulis, histogenesis, immunohistochemistry, newborn.

Introduction

Congenital epulis is a rare benign soft tissue lesion exclusively occurring on the alveolar ridge of the newborns. It occurs eight times more frequently in females; and the maxilla is three times more commonly affected than the mandible (Fuhr and Krogh, 1972). The lesion was first described by Neumann in 1871 and is synonymous with congenital gingival granular cell tumour (Rohrer and Young, 1982; Zarbo *et al*., 1983; Takahashi *et al*., 1990), gingival granular cell tumour of the newborn (Lack *et al*. 1982) and congenital granular cell epulis (Vered *et al*., 2009). The latest WHO classification on head and neck tumours uses the term congenital granular cell epulis (Barnes *et al*., 2005).

The exact origin of congenital epulis is still debatable. Previous studies (Lack *et al*., 1981; Zarbo *et al*., 1983; Takahashi *et al*., 1990; Vered *et al*., 2009) were using immunohistochemistry and electron microscopy to determine the histogenesis of this lesion. The aim of this article is to report the immunohistochemical findings of 12 cases of congenital epulis and discuss the literature review.

Materials and methods

A retrospective study was carried out on all congenital epulis cases diagnosed in the Stomatology Unit, Institute for Medical Research, Kuala Lumpur, Malaysia from 1967 to 2014. Information regarding the age at presentation, gender, race, clinical presentation and diagnoses were retrieved from the Oral Pathology Information System (OPIS) computerised data. We could not get information on the mode of treatment since this information was not written by the clinicians in the biopsy

request form. The haematoxylin and eosin (H&E)-stained sections were reviewed and paraffin-embedded tissue blocks were retrieved for immunohistochemical staining. The antibodies used were CD34, CD68, S100 protein, vimentin, CD1a, muscle specific actin, smooth muscle antigen and desmin. The staining was performed according to the standard protocol using the EnVision™ (Dako, USA) system method.

Results

All of the 12 cases accessioned had occurred in females with the age of presentation ranging from 2 days to 90 days (mean age=16 days). The patients comprised of 6 Malays, 3 Chinese, 2 Indians and 1 Orang Asli. Most cases (n=7) had occurred on the maxillary ridge and five cases at the mandibular ridge. Eight cases were presented as pedunculated well-defined lump. The measurement of the growth varied from 0.8 to 4.0 cm. Excisional biopsy was performed for all of the cases. The patients' clinicopathological characteristics are summarized in Table 1.

Microscopically, all of the cases had showed similar typical features. The lesion is surfaced by stratified squamous epithelium with no obvious rete ridges (Fig. 1) and composed of sheets of densely packed polygonal cells with granular eosinophilic cytoplasm and small vesicular nuclei (Fig. 2). Interstitial cells with elongated spindle-shaped morphology were seen in between the granular cells. Focal infiltration of inflammatory cells was also seen; while in two cases, a few scattered odontogenic epithelium cell rests were present. In the larger specimens, ulceration was also noted.

Immunostaining was only carried out in ten cases as there was no sufficient tissue remained. The findings of the presence of immunohistochemistry staining are summarised in Table 2. In all of the cases, the lesional cells were negative for CD34, muscle specific antigen, smooth muscle actin and desmin; while all were positive for vimentin (Fig. 3). Although the granular cells were negative for S100 protein, in five cases there were some cells which were positive for the antibody and these cells were confirmed to be of Langerhan's cells. Interestingly in all the ten cases, the interstitial cells were highlighted by CD68 (Fig. 4).

Table 1 Clinicopathological features of 12 cases of congenital epulis

No.	Race	Gender	Age Presented	Site	Size (Greatest Dimension)
1	Chinese	female	7 days	maxillary ridge	0.8 cm
2	Chinese	female	6 days	mandibulary ridge	1.5 cm
3	Malay	female	12 days	mandibulary ridge	1.2 cm
4	Malay	female	2 days	maxillary ridge	4.0 cm
5	Chinese	female	11 days	maxillary ridge	1.5 cm
6	Malay	female	30 days	mandibulary ridge	2.2 cm
7	Malay	female	2 days	maxillary ridge	2.5 cm
8	Indian	female	2 days	maxillary ridge	2.8 cm
9	Malay	female	11 days	mandibulary ridge	2.7 cm
10	Indian	female	14 days	maxillary ridge	3.0 cm
11	Orang Asli	female	90 days	mandibulary ridge	1.5 cm
12	Malay	female	5 days	maxillary ridge	2.8 cm

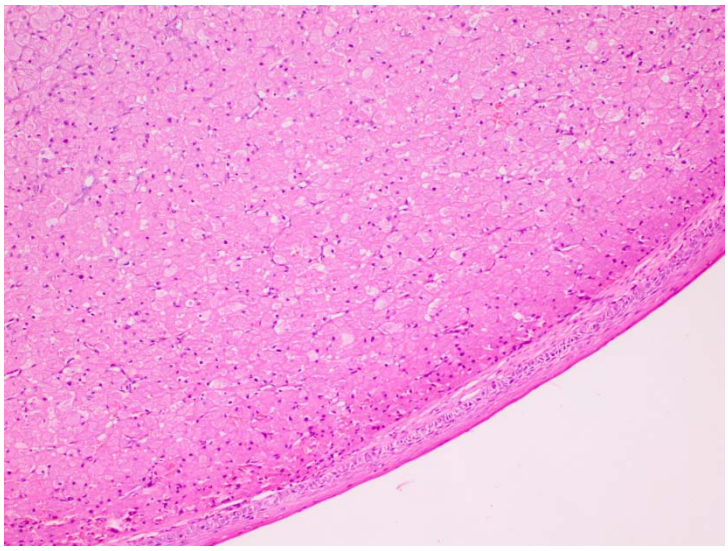

Fig. 1 Congenital epulis is surfaced by stratified squamous epithelium without rete ridges (H&E x10).

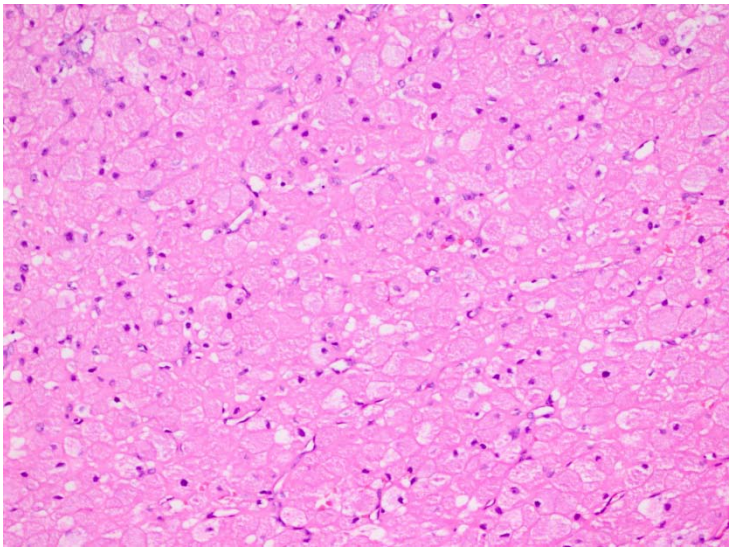

Fig. 2 Sheets of densely packed polygonal cells with granular eosinophilic cytoplasm and small vesicular nuclei (H&E x20).

Table 2 Immunohistochemical findings of 10 cases of congenital epulis

No.	SMA	MSA	CD68*	DESMIN	CD34	VIMENTIN	CD1a	S100
1	-ve	-ve	+ve	-ve	-ve	+ve	+ve	+ve
2	-ve	-ve	+ve	-ve	-ve	+ve	+ve	+ve
3	-ve	-ve	+ve	-ve	-ve	+ve	+ve	+ve
4	-ve	-ve	+ve	-ve	-ve	+ve	-ve	-ve
5	-ve	-ve	+ve	-ve	-ve	+ve	-ve	-ve
6	-ve	-ve	+ve	-ve	-ve	+ve	-ve	-ve
7	-ve	-ve	+ve	-ve	-ve	+ve	+ve	+ve
8	-ve	-ve	+ve	-ve	-ve	+ve	+ve	+ve
9	-ve	-ve	+ve	-ve	-ve	+ve	-ve	-ve
10	-ve	-ve	+ve	-ve	-ve	+ve	-ve	-ve

* positivity seen in the interstitial cells

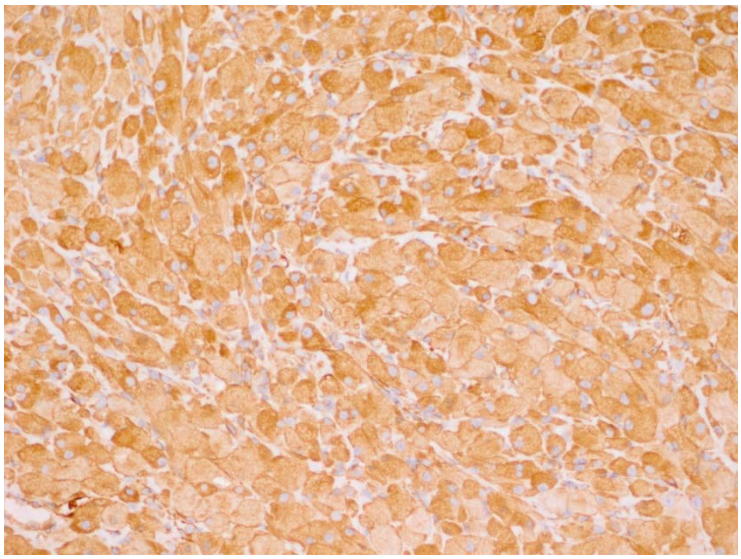

Fig. 3 Granular cells are positive with vimentin (x20).

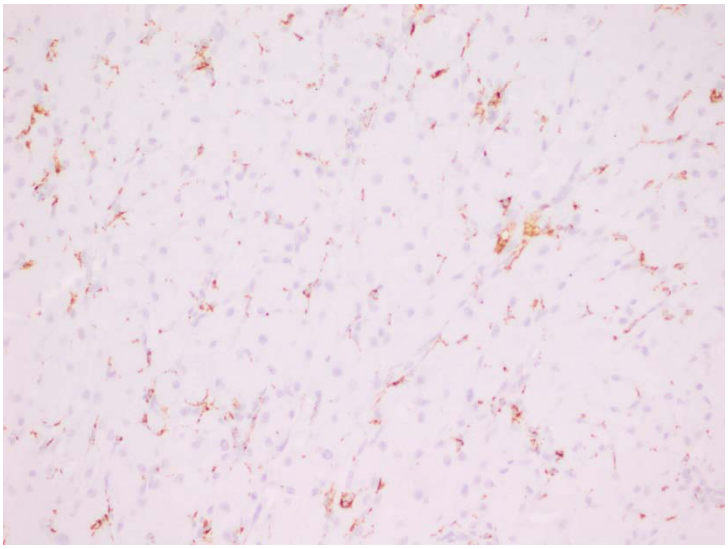

Fig. 4 Interstitial cells are positive for CD68 (x20).

Discussion

Many different terminologies have been used to describe congenital epulis (Lack *et al*., 1982; Rohrer and Young, 1982; Zarbo *et al*., 1983; Takahashi *et al*., 1990; Vered *et al*., 2009). Loyola *et al*. (1997) has disagreed with the term congenital epulis due to the fact that the lesion also occurs on other sites such as the tongue and is not restricted to the alveolar ridge.

Congenital epulis has shown a predilection for females and the present finding was in agreement with the other studies (Custer and Fust, 1952; Lack *et al*., 1981; Zuker and Buenechea, 1993; Küpers *et al*., 2009; Childers and Fanburg-Smith, 2011). Only seven out of 21 cases of congenital epulis had been reported in males (Lack *et al.,* 1981). The maxillary alveolar ridge is more commonly affected compared to the mandibular ridge (Lack *et al*., 1981; Zuker and Buenechea, 1993; Childers and Fanburg-Smith, 2011), of which, the present study has showed similar findings. The most frequent location was within the future canine or lateral incisor teeth (Lack *et al*., 1981).

Congenital epulis usually presents as solitary lesion predominantly occurring on

the anterior maxillary alveolar ridge; however, multiple sites involvement was also reported (Lack *et al*., 1981; Loyola *et al*., 1997; Childers and Fanburg-Smith, 2011). The average diameter of the congenital epulis was 1.0 cm (Lack *et al*., 1981) and the present study has shown variable sizes; with 4.0 cm being the greatest dimension. The largest dimension was reported to be measured at 7.5 cm in diameter (Lack *et al*., 1981).

Microscopically, congenital epulis consists of large, slightly eosinophilic cells with granular cytoplasm set in a prominent vasculature with no cellular or nuclear pleomorphism seen (Barnes *et al*., 2005). Odontogenic epithelial cell rests were seen in 2 of the present cases, which has similar finding as reported by Childers and Fanburg-Smith (2011). In a previous study, 3 cases were reported of having epithelial inclusions resembling tooth-bud epithelium (Custer and Fust, 1952). However, in another previous study, no pseudoepitheliomatous hyperplasia or odontogenic rests was reported in their 5 cases (Vered *et al.*, 2009).

Research on the histogenesis of congenital epulis is still ongoing. Many different theories on the origin of the lesion have been suggested including mesenchymal (Lack *et al*., 1981; Lack *et al*., 1982), epithelial (Vered *et al*., 2009), muscle (Zarbo *et al*., 1983), neural (Zarbo *et al*., 1983), fibroblastic (Lack *et al*., 1982), pericytes (Rohrer and Young, 1982), and uncommitted nerve-related mesenchymal cells (Lifshitz *et al*., 1984; Takahashi *et al*., 1990; Uğraş *et al*., 1997). Fuhr and Krogh (1972) have outlined five principal theories of origin: odontogenic, fibroblastic, histiocytic, myoblastic and neurogenic. Most of these studies had utilised immunohistochemistry (Monteil *et al*., 1987; Takahashi *et al*., 1990; Damm *et al*., 1993; Kaiserling *et al*., 1995; Uğraş *et al*., 1997; Vered *et al*., 2009; Childers and Fanburg-Smith, 2011) and electron microscopy (Lack *et al*., 1982; Rohrer and Young, 1982; Zarbo *et al*., 1983; Damm *et al*., 1993; Kaiserling *et al*., 1995) to demonstrate the histogenesis. Zarbo *et al*. (1983) had found smooth muscle differentiation ultrastructurally which exhibited S100 negativity immunohistochemically. Other previous studies (Takahashi *et al*., 1990; Uğraş *et al*., 1997; Damm *et al*., 1993; Lazaris *et al*., 2000) showed the cells were positive for neuron specific enolase (NSE) and vimentin.

Some morphologic features of the congenital epulis are shared by the granular cell tumour previously known as granular cell myoblastoma. The present immunohistochemical findings show all the muscle markers were negative and this led to the evidence against the congenital epulis as having a muscle cell origin. On the other hand, vimentin is positive in all of the present cases. Vimentin is a marker of intermediate filament in cells of mesenchymal origin. Granular cell tumour is positive with S100 protein but congenital epulis do not exhibit positivity with S100 protein (Kaiserling *et al*., 1995). The negativity for S100 protein thus distinguishes congenital epulis from the granular cell tumour (Kaiserling *et al*., 1995; Ajura and Lau, 2008; Childers and Fanburg-Smith, 2011). Microscopically, the granular cells in congenital epulis are more closely and homogenously packed; showing more variation in shape and are more vascular than granular cell tumour (Odell and Morgan, 1998). Additionally, the congenital epulis is more uniform in structure; contains no demonstrable neural components; has no pseudoepitheliomatous hyperplasia and has more prominent and distinctive vascular components compared to granular cell tumour (Custer and Fust, 1952).

According to Takahashi *et al*. (1990), the immunophenotype of congenital epulis is in biphasic pattern and they had interpreted the interstitial cells as to have exhibited neuroendocrine differentiation. In another study (Damm *et al*. 1993), the cells were positive for leucocyte common antigen (LCA) and lysozyme. Additionally, in other studies (Vered *et al*., 2009; Kaiserling *et al*., 1995) the interstitial cells were reported to be positive for S100 protein, macrophages markers (CD68), calretinin; and negative for neuron specific enolase (NSE). They had suggested these cells as to have represented the earlier stage of the granular cells and lose reactivity to S100 protein and also to CD68 antibody during the transition

to an entire granular morphology. In all of the present cases, the interstitial cells were highlighted by CD68. CD68 is a lysosomal antigen which is expressed at high levels in monocyte/macrophage; and at lower levels in immature skin Langerhans cells; and is down-regulated on maturation (Geissmann *et al*., 2001).

Monteil *et al*. (1987) had highlighted S100 positivity for smaller, isolated spindled or stellate nongranular cells distributed in the periphery of some blood vessels. Cells which were stained positively with S100 protein in the present study were also stained with CD1a, a marker for Langerhan cells (Hicks and Flaitz, 2005). In a previous study (Vered *et al*., 2009), immunohistochemistry markers were used on congenital epulis; 93% of the cases were positive with vimentin and 48% cases were immuno-positive with NSE. In the present study, NSE was not applied since the antibody has been found to be expressed in a wide range of cells and tumours (Leong, 1993). Other newer markers which have shown positivity are PGP9.5 (neurogenic) and NKI/C3 (mesenchymal) (Vered *et al*., 2009). CD34 is a transmembrane phosphoglycoprotein and regarded as a marker of hematopoietic stem cells and hematopoietic progenitor cells (Sidney et al., 2014). In the present cases, the cells were negative for CD34, thus ruling out vascular lesion.

Although congenital epulis is a benign lesion, parents are usually alarmed and anxious of the clinical presentation in their newborns. A majority of congenital epulis is surgically excised as it usually interferes with feeding and sometimes respiration. In a report by Lack *et al*.(1981), two newborns had feeding difficulties and another experienced intermittent stridor and dyspnea. No recurrence has been reported after simple surgical intervention. Follow-up on 15 patients, which included 11 cases of incomplete resection showed no local recurrence (Lack *et al*., 1981). Spontaneous regression of the lesion was reported (Küpers *et al*., 2009). Lack *et al*. (1981) had noted in their 24 cases, that tumours were usually smaller in patients treated later in the neonatal period. However, this regression of congenital epulis was not evident in the present cases. Furthermore, the average size of congenital epulis in the present cases was larger (2.2 cm) as compared to the size of 1.0 cm as previously reported (Lack *et al*., 1981). Rohrer and Young (1982) and Lack *et al*. (1981) had concluded that the lesion is degenerative or reactive rather than neoplastic. Lack *et al*. (1981) had further suggested that it may be modulated partly by endogenous hormonal stimulus which is either maternal or fetal. No estrogen and progesterone receptors were detected to explain the female predominance (Lack *et al*., 1982). Vered *et al*. (2009) had speculated about a local metabolic or reactive change and this is further supported by lack of growth after birth or sometimes regression of the lesion.

Conclusion

Although congenital epulis was first described 130 years ago, the exact nature of its histogenesis remains a mystery.

Acknowledgements

The authors would like to thank the Director General of Health Malaysia and Director of Institute for Medical Research, Kuala Lumpur for their kind permission to publish this paper.

References

Ajura AJ, Lau SH (2008). Oral granular cell tumour: a clinicopathological study of 7 cases and a brief review of the literature. *Malays Dent J*, **29**(2): 94-96.

Barnes L, Eveson JW, Reichart P, Sidransky D (eds.) (2005): *World Health Organization Classification of Tumours. Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press. p. 198.

Childers EL, Fanburg-Smith JC (2011). Congenital epulis of the newborn: 10 new cases of a rare oral tumor. *Ann Diagn Pathol*, **15**(3): 157-161.

Custer RP, Fust JA (1952). Congenital epulis. *Am J Clin Pathol*, **22**(11): 1044-1053.

Damm DD, Cibull ML, Geissler RH, Neville BW, Bowden CM, Lehmann JE (1993). Investigation into the histogenesis of

congenital epulis of the newborn. *Oral Surg Oral Med Oral Pathol*, **76**(2): 205-212.

Fuhr AH, Krogh PH (1972). Congenital epulis of the newborn: centennial review of the literature and a report of case. *J Oral Surg*, **30**(1): 30-35.

Geissmann F, Lepelletier Y, Fraitag S, Valladeau J, Bodemer C, Debré M *et al*. (2001). Differentiation of Langerhans cells in Langerhans cell histiocytosis. *Blood*, **97**(5): 1241-1248.

Hicks J, Flaitz CM (2005). Langerhans cell histiocytosis: current insights in a molecular age with emphasis on clinical oral and maxillofacial pathology practice. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*, **100**(2 Suppl): S42-S66.

Kaiserling E, Ruck P, Xiao JC (1995). Congenital epulis and granular cell tumor: a histologic and immunohistochemical study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*, **80**(6): 687-697.

Küpers AM, Andriessen P, van Kempen MJ, van der Tol IG, Baart JA, Dumans AG *et al*. (2009). Congenital epulis of the jaws: a series of five cases and review of literature. *Pediatr Surg Int*, **25**(2): 207-210.

Lack EE, Worshan GF, Callihan MD, Crawford BE, Vawter GF (1981). Gingival granular cell tumors of the newborn (congenital "epulis"): a clinical and pathologic study of 21 patients. *Am J Surg Pathol*, **5**(1): 37-46.

Lack EE, Perez-Atayde AR, McGill TJ, Vawter GF (1982). Gingival granular cell tumor of the newborn (congenital "epulis"): ultrastructural observations relating to histogenesis. *Hum Pathol*, **13**(7): 686-689.

Lazaris AC, Eftychiadis CA, Nicolopoulou P, Paraskevakou HA, Davaris PS (2000). Congenital epulis: an ultrastructural and immunohistochemical case study. *Adv Clin Pathol*, **4**(4): 159-163.

Leong AS-Y (ed.) (1993). *Applied Immunohistochemistry for the Surgical Pathologist.* Boston: Edward Arnold. p. 33.

Lifshitz MS, Flotte TJ, Greco MA (1984). Congenital granular cell epulis. Immunohistochemical and ultrastructural observations. *Cancer*, **53**(9): 1845-1848.

Loyola AM, Gatti AF, Pinto DS Jr, Mesquita RA (1997). Alveolar and extra-alveolar granular cell lesions of the newborn: report of case and review of literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*, **84**(6): 668-671.

Monteil RA, Loubiere R, Charbit Y, Gillet JY (1987). Gingival granular cell tumor of the newborn: immunoperoxidase investigation with anti-S-100 antiserum. *Oral Surg Oral Med Oral Pathol*, **64**(1): 78-81.

Odell EW, Morgan PR (1998). *Biopsy Pathology of the Oral Tissues*. London: Chapman & Hall Medical. pp. 131-132.

Rohrer MD, Young SK (1982). Congenital epulis (gingival granular cell tumor): ultrastructural evidence of origin from pericytes. *Oral Surg Oral Med Oral Pathol*, **53**(1): 56-63.

Sidney LE, Branch MJ, Dunphy SE, Dua HS, Hopkinson A (2014). Concise review: evidence for CD34 as a common marker for diverse progenitors. *Stem Cells*, **32**(6): 1380-1389.

Takahashi H, Fujita S, Satoh H, Okabe H (1990). Immunohistochemical study of congenital gingival granular cell tumor (congenital epulis). *J Oral Pathol Med*, **19**(10): 492-496.

Uğraş S, Demírtaş I, Bekerecíoğlu M, Kutluhan A, Karakök M, Peker O (1997). Immunohistochemical study on histogenesis of congenital epulis and review of the literature. *Pathol Int*, **47**(9): 627-632.

Vered M, Dobriyan A, Buchner A (2009). Congenital granular cell epulis presents an immunohistochemical profile that distinguishes it from the granular cell tumor of the adult. *Virchows Arch*, **454**(3): 303-310.

Zarbo RJ, Lloyd RV, Beals TF, McClatchey KD (1983). Congenital gingival granular cell tumor with smooth muscle cytodifferentiation. *Oral Surg Oral Med Oral Pathol*, **56**(5): 512-520.

Zuker RM, Buenechea R (1993). Congenital epulis: review of the literature and case report. *J Oral Maxillofac Surg*, **51**(9): 1040-1043.