Congenital epulis: immunohistochemical findings of 12 cases

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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

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

<table>
<thead>
<tr>
<th>No.</th>
<th>SMA</th>
<th>MSA</th>
<th>CD68*</th>
<th>DESMIN</th>
<th>CD34</th>
<th>VIMENTIN</th>
<th>CD1a</th>
<th>S100</th>
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<tr>
<td>1</td>
<td>-ve</td>
<td>-ve</td>
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<td>-ve</td>
<td>-ve</td>
<td>+ve</td>
<td>+ve</td>
<td>+ve</td>
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<tr>
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<tr>
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<td>-ve</td>
<td>+ve</td>
<td>-ve</td>
<td>-ve</td>
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<td>+ve</td>
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<tr>
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<td>-ve</td>
<td>-ve</td>
<td>+ve</td>
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<td>-ve</td>
</tr>
<tr>
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<td>-ve</td>
<td>+ve</td>
<td>-ve</td>
<td>-ve</td>
<td>+ve</td>
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<td>-ve</td>
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<tr>
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<td>-ve</td>
<td>+ve</td>
<td>-ve</td>
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<td>+ve</td>
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<tr>
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<td>-ve</td>
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<td>-ve</td>
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<td>+ve</td>
<td>-ve</td>
<td>-ve</td>
</tr>
<tr>
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<td>-ve</td>
<td>-ve</td>
<td>+ve</td>
<td>-ve</td>
<td>-ve</td>
<td>+ve</td>
<td>-ve</td>
<td>-ve</td>
</tr>
</tbody>
</table>

* positivity seen in the interstitial cells
**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.

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