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Congenital Granular Cell Epulis: A Systematic Review of Cases from 2000-2017

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Abstract

Background: *Congenital Granular Cell Epulis is a rare benign mesenchymal tumor that is usually present at birth as incidental finding, however, with the advances in the imaging technology, the prenatal diagnosis of the lesion is possible as early as at 26th weeks.*

Objective: *The aim of this review was to describe the overall pattern of occurrence and clinical presentation of CGCT, to determine if there are any risk factors associated with occurrence of CGCE, and determine the appropriate treatment time.*

Methods: *We searched electronic databases (Google Scholar, DOAJ, PubMed and Mendeley) to identify case reports of patients with congenital epulis from year 2000 through 2017. Criteria to accept the article included case reports and case series that had information about the patient's sex and location of the tumor and a histological diagnosis.*

Results: *A total of 124 publications met inclusion criteria reporting on 156 cases. The region of Asia had majority of reported cases followed by Europe. Majority of the infants were born on term without any reported complication during pregnancy. The female to male ratio was 7.7:1.The maxilla to mandible ratio was 1.7: 1. In majority of the cases the lesion was solitary and predominantly occurred on the anterior aspect of the jaws. The most common complication due to the tumor was feeding difficulty. Majority of the cases were documented to have been managed surgically within a week postpartum.*

Conclusion: *Despite being a rare condition, whose diagnosis is suspected clinically but histopathological investigation is mandatory in the diagnostic process. Surgery can be done as early as few hours after birth, with no major post-operative complications.*

Keywords: *Congenital Granular Cell Epulis, Infant, maxilla, systematic review.*

INTRODUCTION

Congenital Granular Cell Epulis (CGCE), initially defined as "congenital epulis" by Ernst Christian Neumann in 1871, is a rare benign mesenchymal tumor [1]. Since it was first described by Neumann, it is also termed as the Neumanns' Tumor [2]. There are many other names for this condition such as congenital epulis, congenital granular myoblastoma, congenital granular cell fibroblastoma and congenital granular cell tumor [3].

CGCE are usually present at birth as incidental finding [4], but with the advances in the imaging technology, the prenatal diagnosis of the lesion can be possible as early as 26 weeks [3]. The estimated incidence for its occurrence is just 0.0006% [2, 5]. They have been reported to be three times more common in the maxillary alveolus than in the mandibular alveolus [6, 7]. Females have been reported to be more affected, with literature citing the female: male ratio of 4:1 to 10:1 [3, 7–9].

The etiology of the condition is unknown. Several theories have been suggested to explain its origin, namely, myoblastic, odontogenic, neurogenic, fibroblastic, histiocytic and endocrinologic [6]. Other theories of origin include: epithelial, undifferentiated mesenchymal cell, pericytes, smooth muscles, nerve related cells and myofibroblasts [8].

CGCE shows a benign behavior and usually presents as a pedunculated, non-ulcerated, reddish pink mass of varying sizes [7, 10]. It is mostly solitary, but multiple lesions are seen in 10% of the cases with simultaneous involvement of both maxilla and mandible [3, 4]. The recommended treatment is surgical excision though spontaneous regression is known to occur [3], and no recurrence or metastasis has been reported [10].

The aim of this review was to describe the overall pattern of occurrence and clinical presentation of CGCT, to determine if there are any risk factors associated with occurrence of CGCE, and determine the appropriate treatment time.

Methodology

Data Sources and Searches

We searched electronic databases (Google Scholar, DOAJ, PubMed and Mendeley) to identify case reports of patients with congenital epulis from year 2000 through 2017. During the initial literature search no language restrictions were applied. References of included articles were also searched manually. Search words used included congenital epulis, congenital granular cell tumor, oral tumors in newborn, and Neumann's tumor.

Study Selection

The screening of eligible publications was carried out independently by two raters. First, the titles and abstracts of all citations were reviewed. Next, the full texts of potentially relevant citations were reviewed. Discrepancies were resolved by consensus. Cases were only included if they reported patients with a histological diagnosis of congenital granular cell epulis. Studies were excluded if they reported cases of congenital epulis with spontaneous regression since they had no confirmed histological diagnosis. Thus, we used following criteria to accept the article (1) only case reports and case series were to be included. (2) The patient's sex and location of the tumor was mandatory (3) an accurate diagnosis (i.e. histologically diagnosed lesion and not clinical diagnosis).

Data Extraction

Data were extracted by one reviewer and crosschecked by another. Data from articles published in languages other than English were excluded. The information that was extracted from the selected articles included: year of publication, the country from where the case was reported, whether the infant was full term or not, age of the mother, any medical history/complication during pregnancy, sex of the child, location of the tumor, number of lesions, size of the tumor, any associated medical condition in the newborn, when was the surgery done and whether it was under general anesthesia or local anesthesia. Possible item ratings were yes and no.

Data Synthesis and Analysis

Data were summarized using descriptive statistics, with means and standard deviations for continuous variables and frequencies and percentages for dichotomous variables. The countries were divided into 8 region as per Rosenberg division [11].

Results

Publication Characteristics

A total of 5405 literature were initially retrieved from the search, of which 3542 remained after removal of duplicates. A total of 172 case reports were identified as potentially relevant and reviewed the full publication. Forty eight publications of CGCE were excluded on the basis of lacking final histological proof, lacking patient's information of interest, and/or being a review article. Finally, 124 publications were reviewed, with a total of 156 documented cases whose descriptions were provided separately (Figure 1, appendix 1).

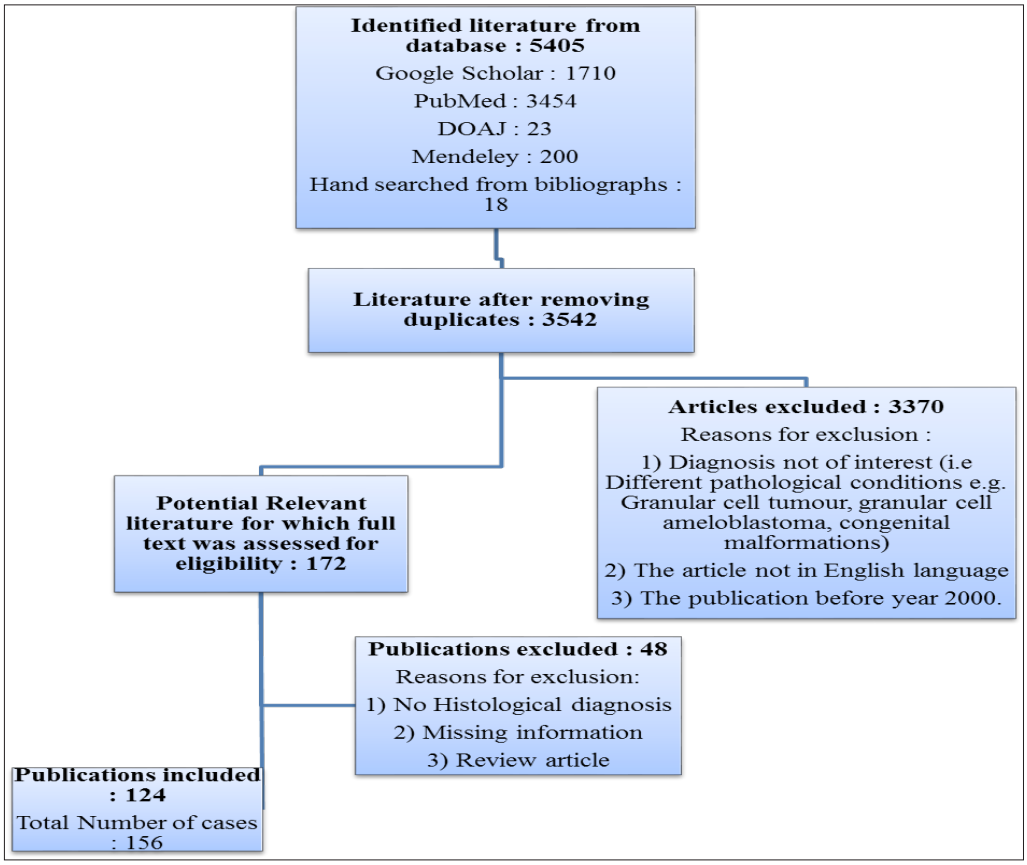

Figure 1. *Literature selection flow chart.*

Majority of the cases were reported from India (20.5%), followed by Malaysia (8.3%), United States (7.7%), China (7.1%), and Brazil (6.4%). Overall, the region of Asia had majority of reported cases followed by Europe, while the region of Australia & Oceania had least number of reported cases (Figure 2).

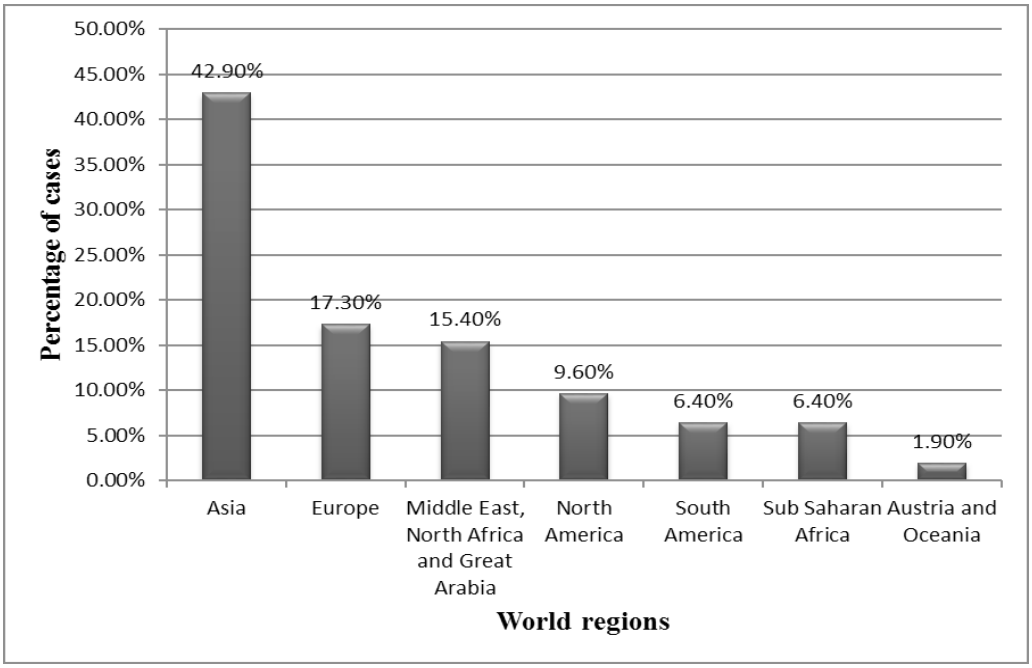

Figure 2. *Distribution of CGCT cases by different World regions*

Maternal and Pregnancy characteristics

Out of the 156 cases of CGCE, 120 cases (76.9%) reported on whether or not the child was born on term. Of these only 6 cases were born on preterm. The age of the mother was documented in only 31 cases (19.9%). The age range was 19-40 years with mean age of 28.9 ± 6.1 years.

Regarding gravidity of the mother, only 38 cases had documented about it, of which, in 21cases (55.3%) the mother was multigravida. Medical history/ complications during pregnancy were documented in 6 cases, of which gestational diabetes was reported in 2 cases. Others included pre-eclampsia, premature rupture of membrane, placental hematoma and HIV/AIDS.

Clinical Characteristics

Majority of the cases occurred in female infants (88.5%). The female to male ratio was 7.7:1. In majority of the cases (80.1%), the lesion was solitary. Almost all cases (99.4 %) had the lesions on the anterior aspect of the jaw.

The occurrence of the lesion on the maxilla was reported in 108 (69.2%) cases while in mandible, it was reported in 62 (39.7%) cases, thus maxilla to mandible ratio is 1.7: 1. Other sites that were documented included the tongue, 5 (3.2%) cases and the palate, 1 case.

Of all the cases, the nature of the lesion was recorded in 140 cases. Of which, 121 (77.6%) were pedunculated. The size of the lesion ranged from 3mm to 80mm, with a mean of 29 ± 16mm.

Regarding the complications arising due to the lesion, in 85.1% of the cases, the child presented with difficulty in feeding. Difficulty in breathing/ upper airway obstruction was reported in only 9.3% of the cases. Associated medical conditions were reported in only 4 cases, and these included one case of each: anemia, intra-ventricular defect, tetralogy of Fallot, and respiratory distress syndrome.

Treatment

All the cases that had been included in this review underwent surgical management of the lesion. In 110 cases (70.5%) description of type of anesthesia used was given. General anesthesia was used in 70 cases (63.6%) while, surgical management by use of local anesthesia was instituted in 39 cases (35.5%). In one case, surgical management was done without using anesthesia.

The timing of surgery ranged from day 1 postpartum to 25 months postpartum. Majority of the cases were documented to have been managed surgically within a week postpartum (71.7%), while 56% of all the surgical management was carried out within 3 days postpartum.

In almost all the case reports, there was very minimum blood loss during the procedure, regardless the type of anesthesia used. Moreover, none of the case reports reviewed documented recurrence of the lesion once surgical management was carried out.

Discussion

Congenital Granular Cell Epulis (CGCE) was first described by Neumann in 1871, who coined the term 'congenital epulis' after the Greek word epoulis meaning 'gumboil' [12]. It is a rare benign intra-oral tumor, which mostly occurs along the gingiva of the alveolar ridges of the newborn [13]. There are many other terminologies for this condition such as congenital epulis, congenital granular myoblastoma, and congenital granular cell fibroblastoma [3]. The term congenital epulis is commonly used by pathologists, however, in the recent World Health Organization classification of the head and neck tumors, this lesion has been named as "congenital granular cell epulis" [14].

CGCE has been described as a rare lesion in several case reports, with an estimated incidence for its occurrence of just 0.0006% [2, 5]. The findings of this systematic review of literature support the rarity of the CGCE, considering that less than 200 cases in English literature have been documented worldwide in range of 17 years.

In this systematic review, it was found that the region of Asia had majority of reported cases of CGCE followed by Europe, while the region of Australia & Oceania had least number of reported cases. Though it may indicate that Asians suffer most, but the findings may also be attributed to the fact that Asia region has the largest population in the world [15] and there by chances of encountering such rare conditions are higher and opposite holds true for the region of Australia & Oceania.

The findings of this systematic review indicate that the majority of infants diagnose with CGCE are born

on term. Furthermore, neither the age of the mother, her gravidity status, nor pregnancy complications/ medical history play part as risk factor for occurrence of this tumor.

The etiology of CGCE remains unknown and controversial and thus several theories have been suggested [6, 8]. However, in search of the origin of the granular cells, a broad panel of antibodies that characterize different tissues failed to determine the tissue of origin for the granular cells in the CGCE, thus leading to some authors assuming these lesions are the result of a degenerative process affecting mesenchymal stem cells [16]. Other authors support a theory of intra-uterine hormonal stimulus due to predominant female prevalence [17]. Yet still, estrogen and progesterone receptor studies of CGCEs have proved negative, and thus intrauterine growth and the higher female incidence may have different causes [18].

Most of the authors have been citing that maxilla is three times more affected than the mandible. Similarly, in this review, maxilla was more affected than the mandible; however, the ratio was 1.7: 1 and not the reported 3:1. Almost all the lesions were found to occur in the anterior portion of the alveolus of the maxilla or mandible, at the inter-canine region.

Congenital epulis usually occurs as a solitary nodule. However, multiple tumors are occasionally seen. Most authors have been citing that in 10% of cases multiple tumors have been noted on the same or different alveolar ridges [4, 14, 19]. The findings from this systematic review indicate that the occurrence of multiple lesions is as high as almost 20%.

The CGCE are soft tissue lesion that are usually pedunculated pink, firm, non-ulcerated, however, they can be erythematous or ulcerated at times, with their size ranging from few millimeters to few centimeters. Depending on the size it can be asymptomatic or can lead to feeding problems or respiratory distress [3]. The commonest problem arising due to these lesions is interference with feeding, and this is attributed to the anterior location of the tumor in majority of the cases. Respiratory distress secondary to the tumor was reported in less than 10% of the cases. Reason for less respiratory difficulties can be explained by that, the nose, rather than oral cavity is the preferred primary route of breathing in the infant because of its ability to humidify, warm, decontaminate, and regulate the air coming into the lungs [20].

Nearly all neonates with CGCE did not have any associated congenital disease or syndrome. Considering that these lesions have only been diagnosed as early as the 26th week of gestation using advanced imaging techniques such as 3D ultra sound and MRI [21, 22], and likewise, they have been found to exhibit accelerated growth during the third trimester [13, 23], these findings are not surprising since embryogenesis and organogenesis are complete by this time.

Though few studies have reported on spontaneous regression of these tumors [24, 25]. Surgery is the treatment for these tumors [26]. Surgery should not be radical; it minimizes the danger of damaging underlying alveolar bone and developing tooth buds [18]. Despite its typical clinical presentation, diagnosis can be rather difficult, especially when the lesions are multiple or involve extra-alveolar sites. Thus, considering the importance and necessity of a histopathological evaluation, the early surgical excision seems to be the proper management of this lesion [16].

Our systematic review included a comprehensive literature search with specific criteria for inclusion including language and year of publication. Our findings are limited nevertheless by the quality and breadth of the data in the reports, which were not uniform or consistent (e.g. not all cases reported on the age of the mother and gravidity status).

Since case series and reports are uncontrolled, they can suggest hypotheses but cannot establish associations because of lack of statistical inference [27]. Therefore, the evidence provided is not sufficient to recommend systematic screening in every pregnancy, but should alert the physician of the possibility of occurrence of the CGCE in infants.

Conclusion

Despite being a rare condition, CGCE should be included in the differential diagnosis of a mass arising from the gingiva in a newborn. A normal antenatal ultrasound early in pregnancy does not exclude this diagnosis. This lesion can be a striking sight for both parents and healthcare professionals involved in neonatal care. The diagnosis is suspected clinically and treatment by simple surgical removal has a curative effect. In addition, histopathological investigation is accepted the gold standard in the diagnostic process. The surgery can be done as early as few hours after birth, with no major post-operative complications.

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Appendix 1:

Yavuzer et al.	2001	Turkey	1
Lapid et al.	2001	Israel	1
De Lacalle et al.	2001	Spain	1
Kasthuri et al.	2001	Sri Lanka	1
Reinshagen et al.	2002	Germany	1
Inan et al.	2002	Turkey	1
Reinshagen et al.	2002	Germany	1
Nakata et al.	2002	Japan	1
Belal et al.	2002	Kuwait	1
Kumar et al.	2002	USA	2
Wittebole et al.	2003	Belgium	1
Roy et al	2003	Canada	1
Charrier et al.	2003	France	1
Merrett et al.	2003	UK	1
Wam	2003	USA	1
Shaw et al.	2004	USA	1
Dash et al.	2004	India	1
Bagewadi	2004	India	1
Parmigiani et al.	2004	Italy	1
Bilen et al.	2004	Turkey	1
Canavan-Holliday et al.	2004	UK	1
Godra et al.	2004	USA	1
Song	2005	Korea	1
Raissaki et al.	2005	Greece	1
Kannan et al.	2006	India	1
McGuire et al.	2006	Canada	1
Thoma et al.	2006	France	1
Kanotra et al.	2006	India	1
Messina et al.	2006	Italy	2
Kim et al.	2006	South Korea	1
Silva et al.	2007	Brazil	1
Senoo et al.	2007	Japan	1
Fister et al.	2007	Slovenia	1
Narasimhan et al.	2007	USA	1
Pinto et al.	2008	Brazil	1

Cheong et al.	2008	Australia	1
Chiabi et al.	2008	Cameroon	1
Nouri et al	2008	France	1
Kumar et al.	2008	India	1
Mabongo et al.	2008	South Africa	1
Feller et al.	2008	South Africa	1
Kim et al.	2008	South Korea	1
Qannam	2009	Saudi Arabia	1
Williams et al.	2009	Australia	1
Sahu et al.	2009	India	1
Eghbalian et al.	2009	Iran	1
Kupers et al.	2009	Netherlands	4
Olojede et al.	2009	Nigeria	1
Gokhale et al.	2009	Oman	1
Guven et al.	2009	Turkey	1
Bosanquet et al.	2009	UK	1
Diniz et al.	2010	Brazil	1
Dhingra et al.	2010	India	1
Su et al.	2010	China	1
Saeed et al.	2010	Iraq	1
Adeyemi et al.	2010	Nigeria	1
Hamouda et al.	2010	Tunisia	1
Hasanov et al.	2011	Azerbaijan	1
Damante et al.	2011	Brazil	1
Jiang et al.	2011	China	1
Shojaei et al.	2011	Iran	1
Sigdel et al	2011	Nepal	1
Dzieniecka et al	2011	Poland	1
Kayiran et al.	2011	Turkey	1
Steckler et al.	2011	USA	1
Merglová et al	2012	Czech Republic	1
Rehman et al.	2012	UAE	1
Bhat et al.	2012	India	1
Bang et al.	2012	India	1
Ahire et al.	2012	India	1
Bansal et al.	2012	India	1
Hiradfar	2012	Iran	1
Khattala et al.	2012	Morocco	1
Szlachetka et al.	2012	USA	1
Kumar et al.	2013	India	1
Zerener et al.	2013	Turkey	1
Paulo et al	2013	Brazil	1
Gupta et al.	2013	India	1

Nagpal et al	2013	India	1
Kato et al.	2013	Japan	1
Lee et al.	2013	South Korea	1
Paulo et al.	2014	Brazil	1
Nirupama et al.	2014	India	1
Sharma et al.	2014	India	1
Sürmeli-onay et al.	2014	Turkey	1
Sweeney et al.	2014	Australia	1
He et al.	2014	China	1
Liang et al.	2014	China	1
Sharma et al.	2014	India	1
Gupta et al.	2014	India	1
Aparna et al.	2014	India	1
Saki et al.	2014	Iran	1
Kadivar et al	2014	Iran	1
Gnassingbe et al	2014	Togo	1
Garg et al.	2014	UK	1
Ahmad et al	2014	USA	1
Bianchi et al.	2015	Brazil	1
Ottoman	2015	Egypt	1
Jalil et al.	2015	Malaysia	12
Rezende et al.	2015	Brazil	2
Petermann et al.	2015	France	1
Mhaske et al.	2015	India	1
Bhoil et al.	2015	India	1
Chhatrapati et al.	2015	India	1
Kumar et al.	2015	India	1
Nagaveni et al.	2015	India	1
Xavier et al.	2015	India	1
Prabhu et al.	2015	South Africa	1
Kwon et al	2015	South Korea	2
Aresdahl et al	2015	Sweden	1
Wu et al.	2016	China	7
Agarwal	2016	India	1
Sun et al.	2016	Canada	1
Pathak et al	2016	India	3
Das et al.	2016	India	1
Wong et al.	2016	Malaysia	1
Omisakin et al.	2016	Nigeria	2
Krasuska-S?awi?ska et al.	2016	Poland	2
Kaba et al.	2016	Turkey	1
Rajendran et al	2016	UK	1

Lenes-Voit et al.	2016	USA	1
Johnson et al.	2017	USA	1
Rech et al.	2017	Brazil	1
Vinay et al.	2017	Ethiopia	1
Shukla et al.	2017	India	2
Yildirim et al.	2017	Turkey	1
Do carmo et al.	2017	USA	1

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