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Case Report

Congenital granular cell epulis of newborn: importance of prenatal diagnosis

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Summary
Congenital granular cell epulis is a rare benign lesion usually arising as single mass from the alveolar ridge of maxillary bone of female newborns, composed of polygonal granular cells that typically stain negative for S-100, in contrast to the adult counterpart. Larger lesions can disturb breathing and breast-feeding, requiring surgery. Prenatal diagnosis is achieved in few cases, even if this would be important for best management of delivery and therapy. Here we present a case of multiple CGCE in a female newborn discovered at birth, together with a brief review of pathogenesis, differential diagnoses and treatment implications of early diagnosis.

Key words: congenital epulis, granular cell tumor of newborn, oral tumors, infancy tumors, benign tumors

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Conflict of interest
The Authors declare no conflict of interest.

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Introduction

Congenital granular cell tumor, congenital epulis or congenital granular cell epulis (CGCE) as suggested by the WHO, was at first described by Neumann in 1871 and since then approximately 250 cases have been reported [1]. It usually presents as a soft lesion arising in the oral cavity, mainly in the maxillary alveolar ridge, followed by the mandibular alveolar ridge [2]. Multiple lesions represent approximately 10% of cases [3]. CGCE can be detected before birth with the aid of ultrasound (US) or magnetic resonance imaging (MRI), because its growth manifests mainly during the third trimester of pregnancy. Despite being a benign lesion, surgery is often needed to allow proper breast feeding in newborns [3]. CGCE is usually represented by a polypoid mass with a wide or thin base covered by pinkish mucosa with 1 to 2 cm as main dimension even cases with a diameter up to 9 cm are reported [3]. The covering mucosa can be erithematous or ulcerated; the latter circumstance along with major dimension can create problems with feeding, breathing and/or with the closure of the mouth, usually leading to an operative surgical approach.[1] On the contrary, small lesions can be managed in a conservative way [1].
Here we present a case of congenital multiple granular cell epulis undetected until the birth of the baby and successfully treated with minimally invasive surgery at five days.

Case presentation

A female term was born through vacuum-assisted delivery with fetal tachycardia during the expulsive period of labor, with cyanosis and an Apgar

score of 7 at 1 minute, requiring ventilator assistance and hospitalization in the neonatal intensive care unit. At physical examination two polypoid lesions covered by pinkish mucosa were found arising from the alveolar ridge of the maxillary bone. The lesions were investigated through computed tomography (CT) and MRI exams that described in particular the major one as a polylobed area, measuring 20x18x16 mm in size, slightly hyperintense on T1-weighted imaging before contrast medium and heterogeneous mild hyperintensity on T2-weighted imaging (Fig. 1A-B). There was no connection with the palatine bone or signs of palatoschisis. Imaging features led to exclude a cystic, lymphatic or angiomatous lesion and were consistent with bone fibromas. Subsequently, at the age of five days, surgical excision was performed without complications. The samples, consisting of a whitish nodule of 1.7 x 1.5 x 1 cm and three smaller fragments, were formalin-fixed and paraffin-embedded, and 5 µm thick sections were cut and stained with hematoxylyn and eosin. Microscopically the lesions were composed of a monomorphic proliferation of large cells with granular cytoplasm, with interspersed abundant vessels and covered by a normal layer of squamous stratified epithelium (Fig. 2A-C). No atypical features were present. At immunohistochemistry the cells were negative for S-100 (Fig. 2D), cytokeratins, synaptophysin, desmin, HMB45, SOX10, CD68. Taken together, clinical, histological and immunohistochemical characteristics were consistent with the diagnosis of congenital granular cell epulis. Informed consent was acquired from the parents for publication of the case. This study was approved by the Institutional Review Board AOUI Verona (ref. No. 1745CESC).

Discussion

CGCE is an important entity to be considered in the differential diagnosis of oral masses in fetuses and newborns. CGCE is rare, benign and arises two to three times as often from the maxillary alveolar ridge as the mandible alveolar ridge, more precisely at the future location of the canin or the lateral incisor [3,4]. It involves more frequently female newborns with a female-male ratio of 10:1 as a single lesion while multiple lesions have been found only in up to 10% of the cases [3]. Histologically CGCE is composed of large polygonal cells with eccentric nuclei, slightly visible nucleoli and abundant eosinophylic granular cytoplasm [3]. Cells are organized in big nests or bands, with interspersed abundant vascular vessels, surrounded by a delicate stromal space, occasionally occupied by chronic inflammatory cells such as lymphocytes [3]. The overlying

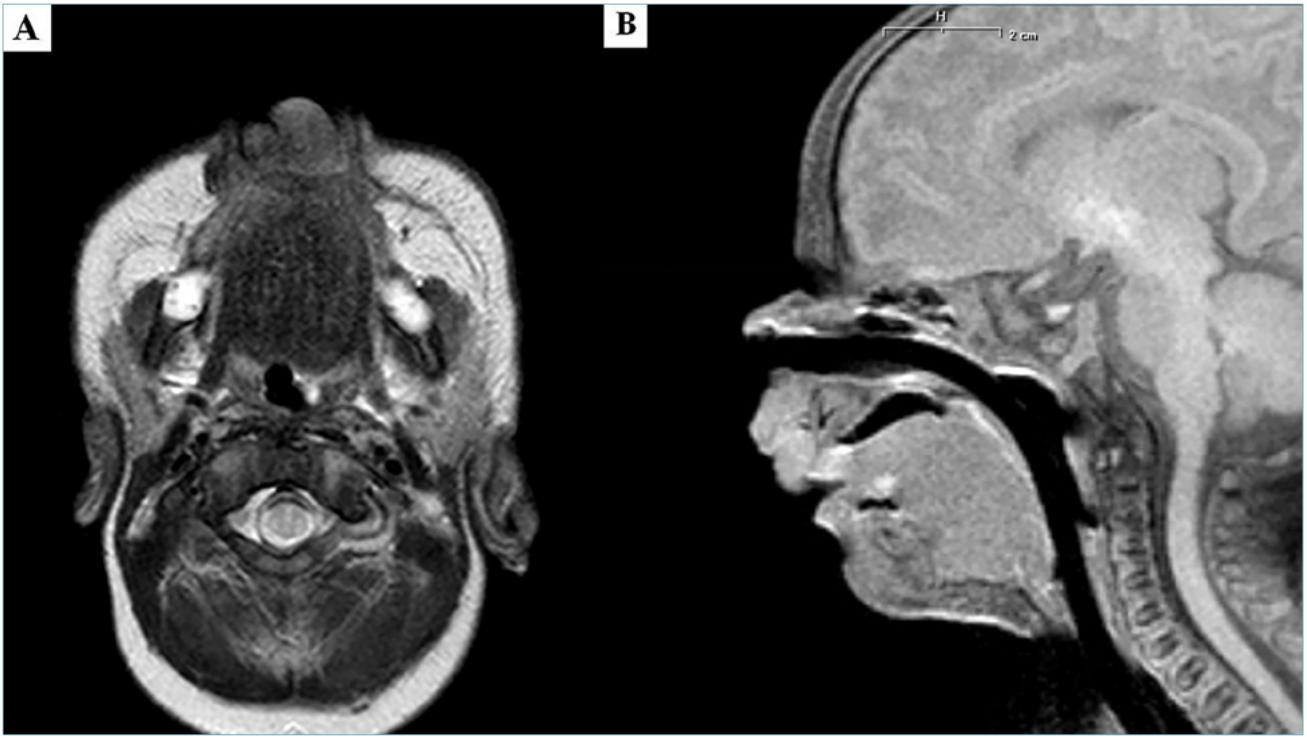

Figure 1. Coronal (A) and sagittal (B) plane MRI scan showing the two contiguous lesions in the alveolar maxillary ridge.

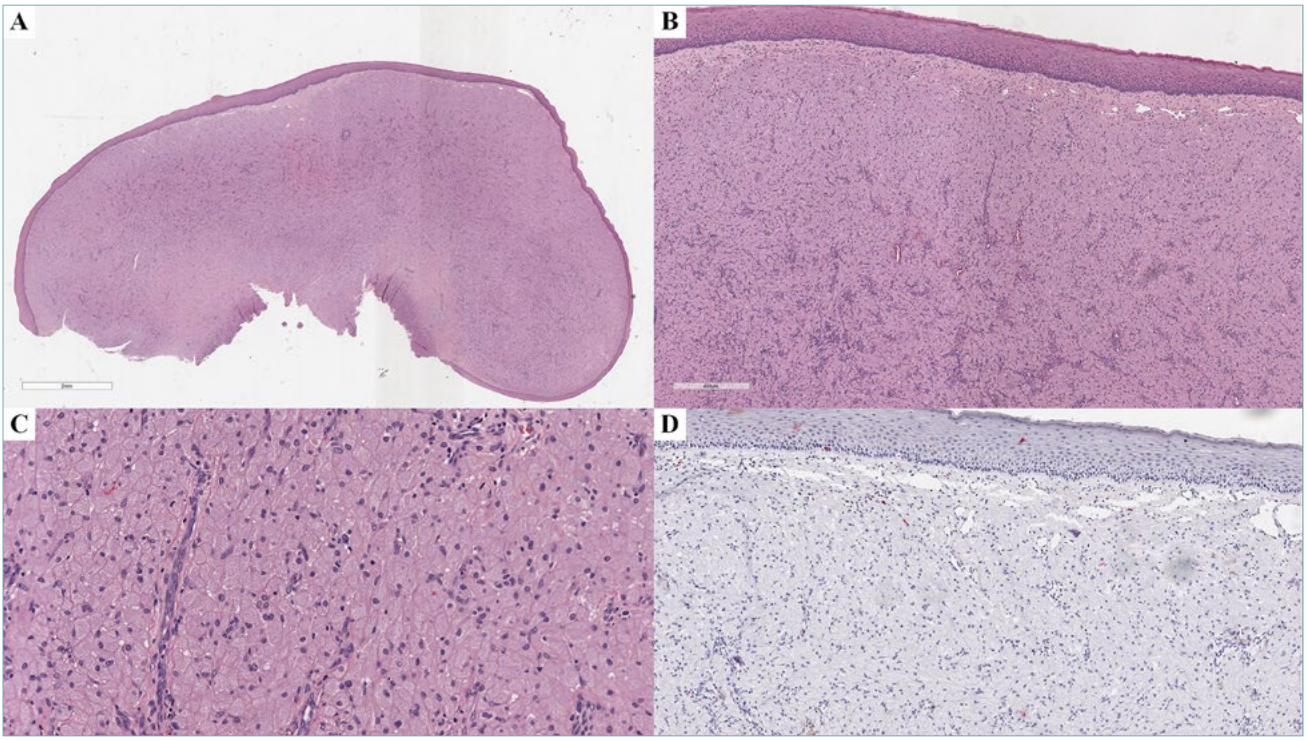

Figure 2. Histological appearance of CGCE, with large polygonal cells with a granular cytoplasm arranged in bands and with no atypical features (A-C). Immunohistochemistry shows negativity for S-100 (D). Original magnification: 1.2x (A), 5x (B), 20x (C), 10x (D).

squamous epithelium is thin with no sign of pseudoepitheliomatous hyperplasia [3]. Congenital granular cell epulis shows immunoreactivity for vimentin and in approximately 40% of cases for neuron specific enolase (NSE) [5,6]. S-100, smooth muscle actin (SMA), desmin, calponin, keratins, chromogranin, inhibin, nerve growth factor receptor (NGFR), CD31, CD34, laminin, CD68 are negative [7,8]. Although our case presented all the classical histological and immunohistochemical features reported in literature, some differential diagnoses have been considered. The main histopathological differential diagnosis of CGCE is with the granular cell tumor of the adult [9]. This lesion occurs typically on the tongue of adults, aged 30 to 60 years old, with 2:1 female-to-male ratio [3]. It consists of a nested or banded proliferation of polygonal granular eosinophilic cells, sometimes with cytoplasmic hyaline globules. Typically these cells stain positive for NSE, CD68 and for S-100 which is the most useful marker for the differential diagnosis with CGCE [3]. Granular eosinophilic cells can be characteristic of other lesions of infancy, such as soft tissue odontoma, which comprises a fibrous and myxoid stroma with dentin, enamel and pulpal elements, or neuroectodermal tumor of infancy which is composed of large peripheral cells, positive for S-100, HMB45 and cytokeratins, and small neuroblastic cells, positive for S-100, GFAP and synaptophysin [10]. In some cases CGCE can show different features, like spindled cells and well-developed fibrosis, suggesting primarily other differential diagnoses such as rhabdomyoma or infantile myofibroma [10]. Rhabdomyoma is a typical heart muscle lesion involving male adults, with head and neck district as the main extra-cardiac location. There is a fetal subtype with spindle cells and an adult subtype with polygonal granular eosinophilic cells. Infantile myofibroma instead involves the tongue or mandible, and is represented by a proliferation of actin-positive spindle cells admixed with a proliferation of hemangiopericytoma-like vascular component [10]. Regarding pathogenesis it has been supposed that maternal hormones play a role in the growth of CGCE, although the presence of estrogen receptors and progesterone receptors in the tumor cells has never been demonstrated [2]. Nonetheless, CGCE grows during the third trimester of pregnancy until birth, suggesting an hormonal, not yet explained, maternal influence [2]. Moreover, after birth in some cases the lesion regresses spontaneously after

a few months and usually do not recur after surgery. Malignant transformation of CGCE has never been reported. Macrophages infiltrating the stromal spaces of the lesion can potentially explain the spontaneous regression and transformation in a fibrous lesion, according to some authors [6]. These characteristics raise doubts about the real nature of CGCE, as some authors tend to consider it of reactive or degenerative nature rather than a true neoplasm [2]. Indeed, there is no a consensus yet on its histogenesis and various theories have been proposed, and the mesenchymal origin, from undifferentiated cells, is considered by far the most plausible one [2,6,11].

Lesions are usually studied through US and MRI to define their nature and their possible effects on the fetus and postnatal implications. Cystic lesions are characterized by an anechoic central area that corresponds to the fluid content. Blood flow pattern is of basic importance to distinguish between a mass with a disorganized pattern flow, suggestive for hemangioma, and a mass with an organized blood flow that helps in excluding an hemangioma [12]. MRI is helpful to delineate the relationship of the lesion with other anatomic structures, like in the case of palatoschisis, even if it remains difficult sometimes to determine a functional assessment of fetal swallowing [12]. In this case, US is more useful, as the absence of a stomach bubble and a bidirectional amniotic fluid flow through the nose raise concerns for obstruction. This is an important indication for a cesarean delivery that gives the possibility to perform an ex-utero intrapartum treatment procedure to resolve airways obstruction while maintaining utero-placental blood flow [12,13]. In the literature one case of obstruction of the oral cavity due to a congenital granular cell epulis leading to polyhidramnios has been reported [12,14]. Larger lesions can cause problems post-birth in swallowing, feeding, breathing and aberrant mouth closure. These conditions, along with ulceration in the surrounding mucosa, usually lead to an operative approach with surgical removal under general or local anesthesia [11].

After reviewing the literature in MEDLINE-Pubmed, we found that multiple cases account for approximately 17% of the total amount of records reporting cases of CGCE, which is higher than the previously reported 10% incidence [3]. Furthermore, even if prenatal diagnosis can be useful for planning management, it is possible with US still in a limited quota of cases, as in literature prenatal diagnoses are clearly reported in only 11% of cases. Given the implications for delivery planning and both for therapeutic options, it would be an important improvement to increase the percentage of prenatal diagnosis.

Our case is a perfect example of the difficulties in detecting with imaging during pregnancy and of the severe consequences in the early days of life. Indeed, the lesion was not discovered during pregnancy, and at birth the baby showed a decreased Apgar score, requiring ventilator assistance due to the breathing obstacle. Postnatal CT and MRI study documented the presence of multiple lesions in the alveolar ridge of the maxillary bone and histological examination excluded malignancy, providing the definitive diagnosis of CGCE. As stressed by many reports, prenatal finding of the lesion could help planning a multidisciplinary management and possible surgical treatment [12-14]. Awareness of the existence of this lesion is necessary to raise a suspicion when performing imaging studies in the third trimester of pregnancy, and at the same time a complete picture with information on site and radiological appearance could be of help for the pathologists to establish the diagnosis, when histological and immunohistochemical features are not entirely straightforward.

In conclusion, CGCE is a rare benign entity, with low tendency to recur and no malignant transformation reported. This entity should be suspected before birth for the important implications in delivery management choices and to prevent surgical overtreatment, keeping in mind that final diagnosis rely on histopathology examination after surgery.

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