Congenital Granular Cell Epulis

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- Congenital granular cell epulis is a rarely reported lesion of unknown histogenesis with a strong predilection for the maxillary alveolar ridge of newborn girls. Microscopically, it demonstrates nests of polygonal cells with granular cytoplasm, a prominent capillary network, and attenuated overlying squamous epithelium. The lesion lacks immunoreactivity for S-100, laminin, chromogranin, and most other markers except neuron-specific enolase and vimentin. Through careful observation of its unique clinical, histopathologic, and immunohistochemical features, this lesion can be distinguished from the more common adult granular cell tumor as well as other differential diagnoses.


Congenital granular cell epulis (CGCE), although infrequently reported in the literature (there are fewer than 250 case reports in the literature), was identified more than a century ago. Neumann first described this lesion in 1871, referring to it as “congenital epulis.” The Greek term epulis literally means “swelling on the gingiva” and is used in dentistry to nonspecifically refer to hyperplastic gingival tissue or gingival tumor mass. Thus, a more specific terminology of “congenital granular cell epulis” is recommended by the World Health Organization. Additional nomenclature for this lesion includes the following: congenital granular cell lesion, gingival granular cell tumor (GCT) of the newborn, congenital epulis of the newborn, congenital granular cell myoblastoma, and granular cell fibroblastoma. In this study, we review the histopathologic features and differential diagnosis of CGCE.

CLINICAL PRESENTATION

Congenital granular cell epulis exclusively occurs in newborn infants, predominately girls (female-male, 9–10:1). It characteristically presents as a solitary polyoid nodule firmly attached to the labial aspect of the dental ridge by a narrow or broad base, and it is 2 to 3 times more common on the upper jaw compared with the lower jaw. Up to 10% of cases may display multiple lesions. Congenital granular cell epulis is typically 1 to 2 cm in diameter, although tumors up to 9 cm have been described. The lesion is often covered by smooth pink mucosa, but it may be erythematous or ulcerated. The bone and teeth are not involved. Congenital granular cell epulis has been diagnosed prenatally by ultrasound as early as 26 weeks’ gestational age and is seen as a well-defined hypoechoic protruding oral mass with a branching vascular pattern.

Congenital granular cell epulis appears to rapidly enlarge during the third trimester of pregnancy, but growth ceases after birth. Because of this third-trimester growth and the female predominance, maternal hormones are surmised to play a role in the development of this tumor. Research demonstrating uterine GCT production in newborn mice injected with estrogen seems to support this view; however, the data cannot be directly extrapolated to CGCE. Additionally, no estrogen or progesterone receptors have been detected in these cells.

PATHOLOGIC FEATURES

Microscopically, CGCE is fairly circumscribed and is composed of nests and ribbons of tightly packed, homogeneous, polygonal to slightly spindled, medium to large sized cells with an eosinophilic granular cytoplasm (Figures 1 through 3). The eccentric nuclei may show slight atypia and small nucleoli, but they have an overall bland appearance. No mitoses are seen. A prominent capillary network and slight thinning of the overlying stratified squamous epithelium with absence of rete ridges are noted. Angulated interstitial cells, cytoplasmic hyaline globules, and small peripheral nerve involvement are seldom seen. Histologic variants of CGCE exist, including variants with increased fibrosis and spindle cell features, as seen in Figure 3, which may suggest the lesion is older or traumatized. Other CGCEs may show stag hornlike vascular channels or occasional nests or cords of odontogenic epithelium interspersed among granular cells. Lymphohistiocytic infiltration may also be seen.

Congenital granular cell epulis characteristically lacks immunoreactivity for S-100 (Figure 4), CD31 (Figure 5), CD34, CD68, laminin, NGFRp75, inhibin-alpha, chromogranin, keratins, desmin, calponin, and smooth muscle actin; positivity is noted for vimentin (Figure 6) and neuron-specific enolase (Figure 7). Electron microscopy has demonstrated intracellular granules (presumably autophagosomes), poorly formed junctional complexes, and occasional long processes with contractile microfilaments. Multiple theories of derivation have been proposed for CGCE, including origination from odontogenic epithelium, neuroendocrine progenitor cells, or mesenchymal progeni-
itor cells, as well as postdegenerative or reactive changes, but its histogenesis is still unknown.\textsuperscript{5}

**DIFFERENTIAL DIAGNOSIS**

The histopathologic differential diagnosis of classic CGCE consists mainly of adult GCT. Adult GCT is a distinct entity that presents in 30- to 60-year-old adults, with a 2:1 female to male ratio, and it is seldom seen in children. The tongue is the frequent location for these painless nodules. Lesions are typically present for less than 6 months, are smaller than 3 cm, and are multiple in approximately 13\% of cases.\textsuperscript{6} Microscopically, adult GCT shows sheets or nests of polygonal eosinophilic granular cells and intermixed angulated interstitial cells. Cytoplasmic hyaline globules may be seen. The overlying squamous epithelium demonstrates pseudoepitheliomatous hyperplasia, and frequent small peripheral nerve involvement is noted. Adult GCT stains for myelin proteins, S-100, neuron-specific enolase, laminin, periodic acid–Schiff with diastase, and CD68/Kp1 (lysosomal marker). They may occasionally recur after surgical excision and very rarely demonstrate malignant transformation.\textsuperscript{6}

Granular cells can also be observed in other lesions, but these are usually excluded from the differential diagnosis based on additional microscopic findings. Soft tissue odontoma may have sheets of granular cells and may occur on the jaw; but, unlike CGCE, it will display a loose myxoid stroma with enamel, dentin, and pulpal elements.\textsuperscript{16} Neuroectodermal tumor of infancy, if lacking its typical melanin pigment, may be confused with CGCE because of a similar nesting pattern and age at presentation; however, it possesses 2 distinct cell types—peripheral large cells (which stain for S-100, HMB-45, and cytokeratin) and small neuroblastic cells (which stain for synaptophysin, GFAP, and S-100).\textsuperscript{16} The rare granular cell odontogenic tumor may also show sheets of granular cells in the gingival region, but it tends to have interspersed odontogenic epithelium and usually occurs in adults.

Some CGCEs may demonstrate nonclassical features, such as fibrosis and spindle cell proliferation (as seen in Figure 3), which may result during trauma or spontaneous regression of the lesion. These features suggest a broader differential diagnostic list that includes reactive changes or spindle cell lesions, such as fibrosing pyogenic granuloma, infantile myofibromatosis, rhabdomyoma, rhabdomyomatous choriostoma, or juvenile xanthogranuloma. Reactive or traumatic changes to normal epithelium would demonstrate inflammation and necrosis while lacking the nested or ribbonlike architecture of CGCE. Fibrosing pyogenic granuloma may have an atrophic or ulcerated overlying epithelium and is composed of a hemangioma-like vascular component in a fibromyxoid matrix. This circumscribed lesion may also contain inflammatory cells, secondary invading microorganisms, stromal edema, brisk mitoses, or fibrosis from involution.\textsuperscript{5,6} Infantile myofibromatosis typically involves the mandible and consists of a circumscribed nodule with short fascicles of actin-positive cells often admixed with hemangiopericytoma-like vessels.\textsuperscript{5,6} Rhabdomyoma is more common in males. Microscopically, the fetal subtype can demonstrate a spectrum of myocyte differentiation, whereas the adult subtype shows polygonal eosinophilic cells with granular cytoplasm, occasional cross-striations, and vacuoles of glycogen. Stains for desmin, muscle-specific actin, and myoglobin are typically positive.\textsuperscript{5}
A rhabdomyomatous choristoma demonstrates histologically normal striated muscle fibers in an abnormal location, often perpendicular to the skin and admixed with adipose tissue, nerves, and vessels. Juvenile xanthogranuloma may show fibrosis if longstanding. Typically, the dermis or soft tissue is infiltrated by sheets of well-differentiated histiocytes expressing CD68, α1-antitrypsin, α1-antichymotrypsin, lysozyme, CD31, and factor XIIIa. Occasional Touton giant cells and inflammatory cells (especially eosinophils) are seen. Correlation of clinical, microscopic, and immunohistochemical findings is helpful in obtaining a correct diagnosis in these cases.

TREATMENT/PROGNOSIS

Congenital granular cell epulis stops growing at birth, occasionally regressing spontaneously. Although frequent monitoring for regression may be used as a management option, conservative excision under anesthesia is the traditional treatment and is especially necessary if the lesion interferes with respiration or deglutition. Rare injuries to dental structures have been reported, although these seem to be secondary to the surgical procedure rather than tumor effects. Congenital granular cell epulis has an excellent prognosis. Lesions seldom recur, even when incompletely excised, and malignant transformation has never been reported. Congenital granular cell epulis has not been associated with any syndromes or genetic defects, so patients have no risk for additional deformities or for passing on germline mutations.

SUMMARY

Congenital granular cell epulis is a rare but distinct entity of uncertain histogenesis. It can easily be distinguished by clinical characteristics (maxillary alveolar ridge of newborn females), microscopic features (granular cells, attenuated overlying squamous epithelium, capillary network), and immunohistochemical pattern (absence of S-100 staining). Recognition of this benign but peculiar lesion is important in achieving correct diagnosis.
References