

CONGENITAL (GRANULAR CELL) EPULIS OF THE NEWBORN: A CASE REPORT WITH IMMUNOHISTOCHEMICAL STUDY ON THE HISTOGENESIS

Pietro Leocata, MD; Giuseppina Bifaretti, MD; Solidea Saltarelli, BS;
Alfonso Corbacelli, MD; Luca Ventura, MD

Congenital epulis (CE) of the newborn is an uncommon lesion, described for the first time in 1871 by Neumann.¹ To date, fewer than 200 cases have been described in the literature.² This lesion, which usually presents at birth, is multiple in 10% of the cases,³ has a distinct predilection for females,⁴ and is most frequently located on the anterior maxillary alveolar ridge. The lesion usually appears as a protuberant mass, sometimes pedunculated, histologically showing characteristic large cells with granular cytoplasm and spindle cells resembling fibroblasts. The histogenesis is still uncertain, but several theories, including origin from epithelial,⁵ undifferentiated mesenchymal cells,⁶ pericytes,⁷ fibroblasts,⁸ smooth muscle cells,⁹ and nerve-related cells, have been proposed.¹⁰

We report a case of CE observed in a newborn male, with immunohistochemical investigation, in order to provide additional information about the histogenesis of this lesion.

Case Report

The patient was a newborn male, 4100 g in weight, 51 cm in length (Crown-Heel), who presented at birth with a pedunculated neoformation on the anterior maxillary ridge, measuring 10x5x5 mm in size. The lesion was excised at four days of age. The excised mass, which consisted of a pink nodule, was fixed in 10% buffered formalin. The specimen was embedded in paraffin to obtain 4- μ m thick sections, and stained with hematoxylin and eosin. Further dewaxed sections were taken for immunohistochemical investigation, using the streptavidin-biotin-alkaline phosphatase method. New fuchsin was used as chromogen. The following antibodies were employed: alpha-fetoprotein (clone C3, Novocastra Lab., Newcastle-upon-Tyne, UK); carcino-embryonic antigen (CEA) (clone Col-1, Biomedica,

Foster City, CA); macrophage marker (clone MAC 387, YLEM, Avezzano, AQ, Italy); lysozyme (polyclonal, Novocastra); CD-68 (clone KP1, Biomedica); NSE (clone 5E2, Biomedica); desmin (clone 33, Biomedica); S-100 protein (clone MIG-5, Biomedica); vimentin (clone V9, Biomedica); muscle-specific actin (clone HHF-35, Biomedica); leukocyte common antigen (clone X16/99, Novocastra); estrogen receptors (clone 1D5, DAKO SpA, Milano, Italy); and progesterone receptors (clone 1A6, DAKO). Positive and negative controls were performed in parallel for all the antibodies tested, and all antibodies were prediluted.

Microscopic examination showed a highly vascularized tissue, mainly composed of nests of polygonal cells, with large clear and granular cytoplasm and a small nucleus. The overlying mucosa showed normal squamous epithelium with focal ulcerations. Also present were infiltrates of polymorphonuclear leukocytes within the neoformation (Figures 1 and 2).

The results of the immunohistochemical investigation were graded as negative (-), weakly positive (+), moderately positive (++) or strongly positive (+++), and are summarized in Table 1. A sharp positivity was observed only for vimentin, whereas desmin appeared focally and moderately positive. All other antibodies were negative. Six years after surgical excision, the patient was well and no local recurrence had been observed.



FIGURE 1. Histological section of congenital epulis with overlying normal epithelium (H&E, 40x).

From the Departments of Experimental Medicine (Drs. Leocata and Bifaretti), Surgery (Dr. Corbacelli), University of L'Aquila, and the Department of Pathology (Drs. Saltarelli and Ventura), S. Salvatore Hospital, L'Aquila, Italy.

Address reprint requests and correspondence to Dr. Leocata: Dipartimento di Medicina Sperimentale, Università degli Studi, via Vetoio, Coppito 2, 67100 L'Aquila, Italy.

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FIGURE 2. High-power magnification of granular cells (H&E, 400x).

Discussion

The term "congenital epulis of the newborn" is widely accepted for this entity, and is preferred to that of "congenital gingival granular cell tumor," which suggests a neoplastic origin, not applicable to these lesions. Moreover, CE does not represent a variant of granular cell tumor (GCT).

Although CE closely resembles GCT on microscopic examination, many important differences are revealed. CE is found almost exclusively on the anterior alveolar ridges of the newborn, whereas GCT is an ubiquitous neoplasm that can occur in all age groups and very rarely affects the gingiva.⁹ Microscopically, the overlying epithelium of GCT displays a characteristic pseudoepitheliomatous hyperplasia, which is always absent in CE.¹¹ Moreover, a malignant variant of CE has never been described, in

contrast to GCT. The CE does not express S-100 protein, a typical marker of Schwann cells, often detectable in GCTs. Nevertheless, GCT is not a single entity.¹² Granular cytoplasmic changes have been described in many different neoplasms and non-neoplastic tissues. Thus, the granular cell is to be considered the result of a metabolic change due to still unknown conditions.

Immunohistochemical features of CE have less variability than GCT. Immunohistochemical results of our case substantially agree with those previously reported, except for some slight differences. Positivity for vimentin is constantly described, whereas occasional positive NSE and CEA staining has been reported.^{2,4,10} CEA staining in our study was also negative, as in other studies.^{4,13} The positivity reported in a few cases is due to a cross-reaction with CEA-like antigens contained in the secondary lysosomes of granular cells, excluding, therefore, an epithelial origin.⁹ Specific macrophage markers (lysozyme, MAC 387, CD 68) were also negative, as reported in other cases.^{4,13} Equally negative, according to the literature,⁵ was the search for alpha fetoprotein. No immunoreactivity was found for S-100 protein and NSE. These markers are, instead, diffusely present in GCT, indicating a derivation from Schwann cells for the majority of them. Several NSE-positive cases of CE have been reported,^{2,4,10} however, it is well-known that this marker lacks neural specificity and cannot furnish sufficient evidence about the histogenesis. Hence, in our opinion, the derivation from uncommitted nerve-related mesenchymal cells is unlikely.

Positive staining was observed for vimentin, which was distributed almost exclusively within the cytoplasm. In the literature, vimentin is constantly present, either in the intercellular spaces or in the cytoplasm of granular cells,^{4,11} and can be explained by the abundance of collagen and its precursors in the tissue. Furthermore, vimentin represents an ideal internal control for monitoring the quality of tissue fixation, which is of great importance in the evaluation of antigen loss induced by tissue processing.¹⁴ As many antigens show strong reactivity in sites of good vimentin preservation, when a sharp expression of vimentin is observed, other immunohistochemical results can be considered highly reliable.

Desmin was focally positive in our study. Desmin, a 53 kD fibrillar protein, is a specific marker for muscle cells. Ultrastructural signs of smooth muscle differentiation were first detected in two cases of congenital epulis in 1983,⁹ and recently confirmed by other authors.^{4,11} Nevertheless, no muscle-specific actin immunostaining was present in our case. Rather than a myofibroblastic differentiation of a mesenchymal lesion, our data probably indicate a stromal-derived lesion containing myofibroblasts. Unfortunately, an ultrastructural study could not be carried out to confirm the myofibroblastic nature of these elements.

The fact that CE arises in the newborn may lead to the hypothesis that maternal hormonal influence is an important factor in the growth of the lesion. As CE

TABLE 1. Immunohistochemical results.

Antibodies	Clone	Source	Results
Alpha-fetoprotein	C 3	Novocastra	-
CEA	Col-1	Biomed	-
Macrophage marker	MAC 387	Ylem	-
Lysozyme	Polyclonal	Novocastra	-
CD 68	KP 1	Biomed	-
LCA	X16/99	Novocastra	-
NSE	5E2	Biomed	-
S-100 protein	MIG-5	Biomed	-
Desmin	33	Biomed	++*
Vimentin	V 9	Biomed	+++
Muscle-specific actin	HHF-35	Biomed	-
Estrogen receptors**	1D5	Dako	-
Progesterone receptors**	1A6	Dako	-

--negative; +=weakly positive; ++=moderately positive; +++=strongly positive; *focal positivity; **after microwave pretreatment; CEA=carcino-embryonic antigen.

normally stops growing at birth, and sometimes has a spontaneous regression and may even undergo regressive histological features in cases not excised early, one may hypothesize the absence of such a maternal factor. The absence of detectable levels of estrogen and progesterone receptors observed in our case is in agreement with other reports, and gives no certain clue for a hormonal stimulation in the histogenesis.^{8,11}

It is not yet clear if congenital epulis of the newborn represents a neoplastic or reactive lesion. The absence of local recurrence even after incomplete excision, the possibility of a spontaneous regression, and the lack of a malignant counterpart all favor a non-neoplastic origin. In spite of the close morphological similarity between this lesion and GCT, doubts regarding its histogenesis also continue, since there are numerous elements leading to the consideration that these two lesions are distinct entities.

Some ultrastructural studies have suggested that CE originates from primitive mesenchymal cells with myofibroblastic differentiation. In particular, reticular fibers, collagen and aggregates of intermediate, fine filaments have been demonstrated.^{11,15} Myofibroblasts which are able to produce both collagen and contractile filaments have been described in various conditions of connective tissue proliferation, either benign or malignant, and have also been identified in many oral lesions.¹⁵

Our immunohistochemical findings are compatible with these studies, and may suggest a derivation from uncommitted mesenchymal cells with a myofibroblastic component. Such mesenchymal cells undergo cytoplasmic granular change for unknown metabolic reasons but retain their immunophenotype. The non-neoplastic origin of CE, which is not necessarily monoclonal, may explain the small variability of immunohistochemical characters reported in the literature.

References

1. Neumann E. Ein fall von kongenitaler Epulis. Arch Heilkd 1871;12: 189-90.
2. Ugras S, Demirtas I, Bekerecioglu M, Kutluhan A, Karakok M, Peker O. Immunohistochemical study on histogenesis of congenital epulis and review of the literature. Pathol Int 1997;47:627-32.
3. Loyola AM, Gatti AF, Pinto DS Jr, Mesquita RA. Alveolar and extra-alveolar granular cell lesions of the newborn: report of a case and review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1997;84:668-71.
4. Damm DD, Cibull ML, Geissler RH, Neville BW, Bowden CM, Lehmann JE. Investigation into the histogenesis of congenital epulis of the newborn. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1993;76:205-12.
5. Kay SER, Wilson MA. Ultrastructural observation on a gingival granular cell tumor (congenital epulis). Cancer 1971;27:674-80.
6. Mirchandani R, Sciubba JJ, Mir R. Granular cell lesions of the jaws and oral cavity: a clinicopathologic, immunohistochemical and ultrastructural study. J Oral Maxillofac Surg 1989;47:1248-55.
7. Rohrer MD, Young SK. Congenital epulis (gingival granular cell tumor): ultrastructural evidence of origin from pericytes. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1982;53:56-63.
8. Lack EE, Perez-Atayde AR, McGill TJ, Vawre GF. Gingival granular cell tumor of the newborn (congenital "epulis"): ultrastructural observations relating to histogenesis. Hum Pathol 1982;13:686-9.
9. Zarbo RJ, Lloyd RV, Beals TF, McClatchey KD. Congenital gingival granular cell tumor with smooth muscle cytodifferentiation. Oral Surg 1983;56:512-20.
10. Takahashi H, Fujita S, Satoh H, Okabe H. Immunohistochemical study of congenital granular cell tumor (congenital epulis). J Oral Pathol 1990;19:492-6.
11. Tucker MC, Rusnock EJ, Azumi N, Hoy GR, Lack EE. Gingival granular cell tumors of the newborn. An ultrastructural and immunohistochemical study. Arch Pathol Lab Med 1990;114:895-8.
12. Ventura L, Guadagni S, Ventura T, Di Silvestre K, Coletti G, Leocata P. Benign granular cell tumor of the breast: a misleading disease. Tumori 1999;85:190-4.
13. Kaiserling E, Ruck P, Xiao J-C. Congenital epulis and granular cell tumor. A histologic and immunohistochemical study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1995;80:687-97.
14. Battifora H. Assessment of antigen damage in immunohistochemistry. The vimentin internal control. Am J Clin Pathol 1991;96:669-71.
15. Schürch W, Seemayer TA, Gabbiani G. The myofibroblast. A quarter century after its discovery. Am J Surg Pathol 1998;22:141-7.