Virchows Archiv A Pathol Anat (1989) 415:403–409

Virchows Archiv A
Pathological Anatomy and Histopathology

Granular cells in odontogenic and non-odontogenic tumours

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Summary. Granular cells can occur in various odontogenic and non-odontogenic tumours. 5 granular cell lesions, one granular cell ameloblastoma, one so-called granular cell ameloblastic fibroma and three granular cell tumours were examined immunohistochemically for the intermediate filaments cytokeratin, vimentin, desmin, neurofilaments and the neural markers NSE and S-100 protein. The granular cell tumors (granular cell myoblastoma) showed positive staining for vimentin and S-100 protein. Only vimentin could be demonstrated in the granular cells of the so-called granular cell ameloblastic fibroma, whereas the granular cell ameloblastoma showed positive staining only for cytokeratin. A positive reaction with S-100 protein was not found in any of the odontogenic tumours. In our opinion the mesenchymal odontogenic granular cell is a fibroblast, whereas the epithelial granular cell is derived from enamel epithelium. The term "granular cell ameloblastic fibroma" is a misnomer, as a number of these tumours are probably central odontogenic fibromas exhibiting granular cell transformation.

Key words: Granular cell – Granular cell ameloblastoma – Granular cell ameloblastic fibroma – Granular cell tumour – Odontogenic fibroma

Introduction

Oxyphil granular cells occur in various rare mesenchymal and epithelial odontogenic tumours, pseudotumours and cysts. A summary of the lesions described to date and their synonyms is shown in Table 1. The most common odontogenic tumour with a granular cell component is the granular cell ameloblastoma, making up 1 to 5% of all ameloblastomas (Hartmann 1974; Kameyama et al. 1987). The granular cells are of epithelial nature and generally occur in the stellate reticulum in the center of the follicular epithelial complexes. The extremely rare granular cell odontogenic cyst is also of epithelial nature (Gold and Christ 1970; Buchner 1973). The congenital epulis (Custer and Fust 1952; Bauer and Bauer 1953) may be observed in newborn children. It occurs most frequently in the incisor region of the maxilla and rarely become larger than 1 cm in diameter. With

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Table 1. Oral granular cell lesions and their synonyms

1	Granular cell tumour
	S: Oral granular cell myoblastoma (Matthews and Mason 1982)
	Abrikossof-tumour
2	Granular cell ameloblastoma
3	Congenital epulis
	S: Congenital granular cell fibroblastoma (Bauer and Bauer 1952)
	Congenital gingival granular cell tumour (Slootweg et al. 1983)
	Gingival granular cell tumour (Kay et al. 1971)
	Gingival granular cell tumour of the newborn (Lack et al. 1982)
4	Granular cell ameloblastic fibroma (Couch et al. 1962)
	S: Central granular-cell tumour of the jaws (White et al. 1978)
	Central granular cell odontogenic fibroma (Vincent et al. 1987)
5	Granular cell peripheral odontogenic fibroma (Lownie et al. 1976)
6	Granular-cell odontogenic cyst (Gold and Christ 1970; Buchner 1973)

the exception of abundant capillary vessels the lesion consists completely of polygonal granular cells. Odontogenic epithelial formations rarely occur (Bhaskar and Akamine 1955). The histogenesis of this lesion is a matter of controversy, the following cells have been considered to be the cells of origin: odontogenic epithelium (Kay et al. 1971; Hoke and Harrelson 1967), "a primitive gingival perivascular mesenchymal cell with potential for smooth muscle differentiation" (Zarbo et al. 1983), "gingival stromal cells with histiocytic and fibroblastic features" (Lack et al. 1982). Custer and Fust (1952) and Sunderland et al. (1983) assume an odontogenic origin.

The granular cell peripheral odontogenic fibroma has been described only once (Lownie et al. 1976). The authors believed that the granular cells in their tumour originated from islands of odontogenic epithelium. The so-called granular cell ameloblastic fibroma (Couch et al. 1962) is characterized morphologically by a stroma of polygonal granular cells, in which elongated, occasionally branched odontogenic epithelial complexes are embedded. The tumour is benign and has been found mostly in elderly women. The histogenesis is a question of controversy.

Congenital epulis (Lack et al. 1972; Kameyama et al. 1983), granular cell ameloblastoma (Tandler and Rossi 1977; Nasu et al. 1984) and so-called granular cell ameloblastic fibroma (White et al. 1978; Takeda 1986) are characterized electron microscopically by closely packed intracytoplasmatic osmiophilic granules which have been interpreted as lysosomes by most authors. The ultrastructural picture answers the description of the granular cell tumour, which is localized most frequently in the tongue, but also occurs in other organs (Enzinger and Weiss 1983). On the basis of immunohistochemical studies it is assumed that this tumour is derived from Schwann cells. The purpose of our study was to compare the expression of various intermediate filaments in granular cell tumours, in granular cell ameloblastoma and in so-called granular cell ameloblastic fibroma.

Material and methods

3 granular cell tumours, 1 granular cell ameloblastoma and 1 so-called granular cell ameloblastic fibroma were examined. The latter developed within the left maxilla in the region 26/27 of a 22 year old male patient and partially occupied the left maxillary sinus. Teeth 26 and 27 had erupted, but were slightly displaced. The largest diameter of the tumour, which was treated surgically by en-bloc resection, measured 4,5 cm.

The granular cell ameloblastoma was located in the right lower jaw of a 22 year old female patient in the region 47 in association with an odontogenic cyst. It was treated surgically by partial resection of the lower jaw. Two of the granular cell tumours developed in the tongue. The male patients were 40 and 62 years of age. A granular cell tumour from the left bronchus of the upper lobe of a 41 year old patient was included as a control.

The tissue was fixed in 4% formalin and embedded in paraffin. Sections from the different tumours were stained with haematoxylin-eosin, elastica van-Gieson and Alcian Blue pH 2,5/PAS. The intermediate filaments anti-cytokeratin – Pan (Boehringer, Mannheim, FRG), vimentin (Camon, Wiesbaden, FRG), S-100 protein (Camon, Wiesbaden, FRG), neurofilament (Camon, Wiesbaden, FRG) and neuron-specific enolase (Camon, Wiesbaden, FRG) were demonstrated immunohistochemically with the Vectastain ABC-method (Camon, Wiesbaden, FRG), linked with peroxidase or alkaline phosphatase. The reactions were carried with and without pretreatment with pronase. The colour substrate for peroxidase was amino-ethylcarbazole (AEC) and Vector-Red for alkaline phosphatase.

Results

Light microscopically of the granular cell ameloblastic fibroma an expansive circumscribed tumour with a narrow pseudo-capsule of connective tissue could be seen. The connective tissue border of the maxillary sinus and the small osseous lamella of the maxilla lay between the tumour and the respiratory epithelium of the left maxillary sinus (Fig. 1a). The main mass of the tumour consisted of voluminous, round to polygonal cellular elements with fine granular cytoplasm. The nuclei were partially centrally and partially peripherally located. A further characteristic of the tumour was very regularly distributed elongated and mostly narrow epithelial complexes consisting of prismatic cells arranged in 2 to 6 layers. A stellate reticulum did not exist. A central lumen was observed in a minority of epithelial complexes (Fig. 1b). The transition of epithelial complexes to granular voluminous cellular elements was very pronounced although a basement membrane could generally not be identified by light microscopy. The granules of the voluminous cells were alcianophilic at pH 2.5. PAS-positive material could be demonstrated in most epithelial complexes, which could not be observed following pretreatment with diastase.

Approximately 95% of the tumour mass showed the structure described above. The rest consisted of structures identical with those of an odontogenic fibroma, exhibiting moderate numbers of fibroblasts and collagenous fibres in a parallel arrangement, with narrow odontogenic epithelial cords embedded between (Fig. 1c, d). The transition to the main tumour mass introduced itself by single round granular cells between the fibre bundles. In the transitional zone cement-like microcalcifications could occasionally be found. Areas of a haemorrhage or necrosis were not seen.

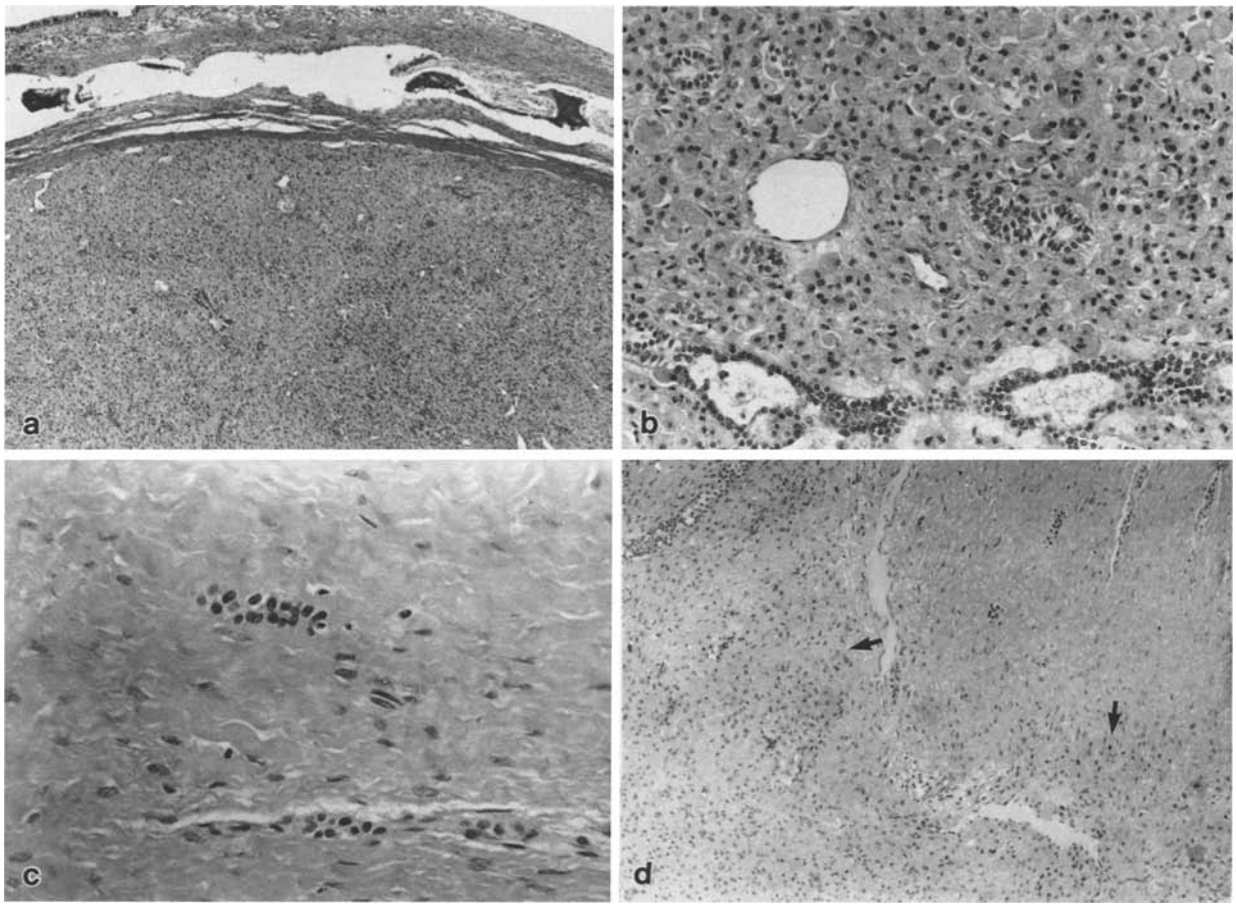

Fig. 1 a–d. "Granular cell ameloblastic fibroma". **a** Overview. Expansively growing intraosseous tumour separated from the maxillary sinus by a narrow zone of bone. EvG. ×40. **b** The tumour consists of elongated, in cross-sections round odontogenic epithelial formations and granular cells. HE. ×130. **c** In small areas the tumour is identical to a central odontogenic fibroma with two-layered epithelial cords. EvG. ×260. **d** The transitional zone between the odontogenic fibroma (*upper right*) and the granular cell areas (*left and below*) is marked with *arrows*. EvG. ×80

The odontogenic epithelial complexes showed positive, the voluminous granular cells negative staining for cytokeratin. The granular cells showed positive, the epithelial complexes negative staining for vimentin (Fig. 2a, b). Moderately large cells with pale cytoplasm lying individually within the epithelial complexes, more seldom amongst the granular mesenchymal cellular elements, showed an intense reaction with S-100 protein. The staining reaction for S-100 protein, desmin, neurofilaments and neuron-specific enolase in the granular mesenchymal cells and in the odontogenic epithelium was negative.

The granular cell ameloblastoma consisted of follicular epithelial complexes and a fibrous stroma. In place of the stellate reticulum there were large cells with eosinophilic finely granular cytoplasm arranged in solid complexes. The slightly hyperchromatic nuclei were located at the periphery of the cell. The outer, palisading, highly prismatic epithelial layers were generally intact (Fig. 3a). The transition of the outer palisading layers to the granular cells was relatively abrupt. Mitoses could be found here, occasionally in the granular cells as well. The AB pH 2.5/PAS reaction was negative. Immunohistochemical reactions with pan-cytokeratin were intensely positive in the granular cells, moderately positive in the outer cell layers (Fig. 3b). The reactions with vimentin, desmin, neurofilament and neuron-specific enolase were negative in all tumour areas. A positive reaction with the antibody S-100 protein could be observed in few cell elements which lay individually within the outer cell layers as well as between the granular cells.

The granular cell tumours in the tongue were located in the subepithelial connective tissue zone and in the striated muscle of the tongue. They consist of large polygonal and round granular cell elements with abundant cytoplasm, which were

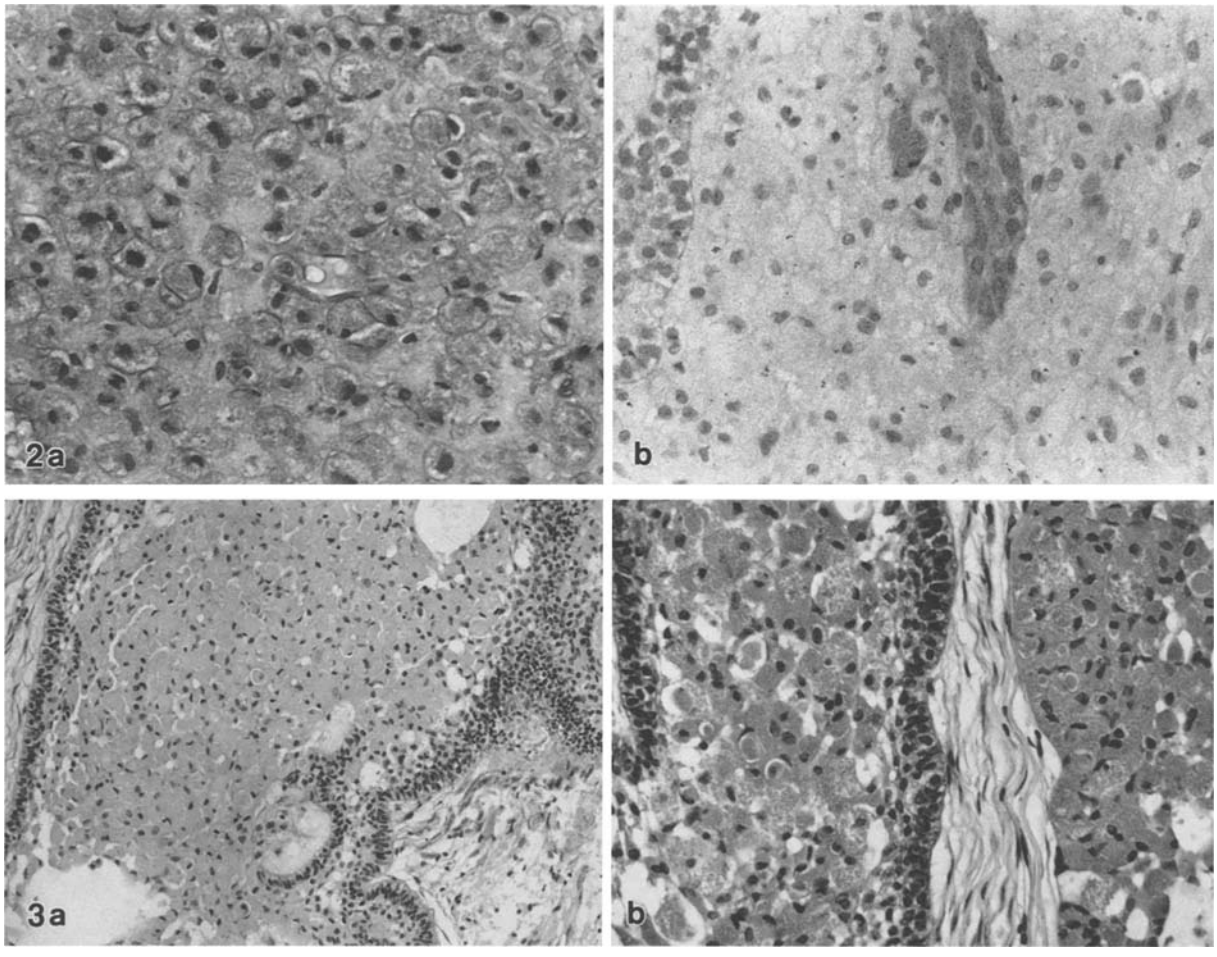

Fig. 2a, b. "Granular cell ameloblastic fibroma". Immunohistochemical reactions. **a** Vimentin. Uniform reaction in the granular cells. ABC-AP, Vector Red. Counterstain haematoxylin. ×275. **b** Cytokeratin. The odontogenic epithelial complexes show a positive reaction, whereas the granular cells do not. ABC-HRP, AEC, Counterstain haematoxylin. ×275

Fig. 3a, b. Granular cell ameloblastoma. **a** Follicular tumor formation. In place of the stellate reticulum there are large granular cells. EvG. ×150. **b** Cytokeratin. Intense reaction in the cellular elements showing granular transformation. ABC-AP, Vector-Red. Counterstain haematoxylin. ×245

packed closely at the centre of the lesion and had replaced the striated muscle almost completely except for a few atrophic muscle fibres. In peripheral areas the tumour cells lay individually or in small groups within the striated muscle and the subepithelial connective tissue. The bronchial granular cell tumour, which served as an immunohistochemical control showed an identical cytological structure. The granular cells were developed in the polypoid thickened tunica mucosa and fibrocartilaginea of the upper lobe bronchus beneath an area of squamous cell metaplasia. This tumour and one granular cell tumour of the tongue were associated with a marked pseudoepitheliomatous hyperplasia. In all 3 tumours the granular cells showed intense staining for S-100 protein (Fig. 4). Staining for the intermediate filament vimentin showed a definitely positive reaction, which varied, however, in intensity. The staining reaction for NSE was not conclusive. The reactions with desmin, cytokeratin and neurofilament were negative.

Discussion

The recent possibility to demonstrate intermediate filaments such as cytokeratin, vimentin and neurofilament as well as neural antigens such as S-100 protein and NSE immunohistochemically has resulted in new knowledge concerning the histogenesis of the granular cell tumours of the oral region and the jaws. With exception of the rarely evident odontogenic epithelial complexes, the morphological structure of the granular cells of the congenital epulis does not distinguish itself from the granular

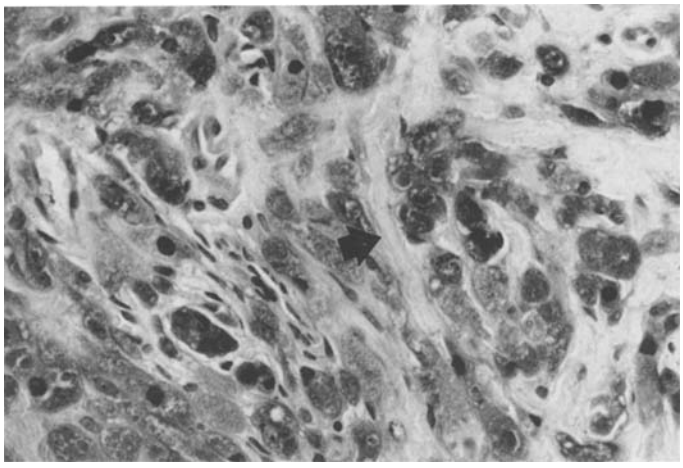

Fig. 4. Granular cell tumor of the tongue. S-100 protein. Intense reaction in the tumour cells. Remaining muscle fibres are negative (*arrow*). ABC-AP, Vector-Red. Counterstain haematoxylin. ×330

Table 2. Intermediate filaments and neural markers in granular cell lesions

Tumour	Cytoker.	Vimentin	Neurof.	Desmin	S-100 P.	NSE	cell of origin
Granular cell tumor	−	+	−	−	+	+/−	Schwann cell
Granular cell ameloblastoma	+	−	−	−	−	−	Enamel epithelium
Granular cell ameloblastic fibroma	−	+	−	−	−	−	Fibroblast of odontogenic mesenchyme
Congenital Epulis	−**	+***	−**	−**	−*	+/−**	Fibroblast of odontogenic mesenchyme

* Lifshitz et al. 1984
** Nahrath and Remberger 1986
*** Slootweg et al. 1983

cell tumour (granular cell myoblastoma). Leaving the different age distribution and the different localisation out of consideration, the immunohistochemical findings also make it probable that their histogenesis is independent from one another. Immunohistochemically the congenital epulis is characterized by postive staining for the intermediate filament vimentin and lacking expression of the intermediate filaments cytokeratin and the neural markers S-100 protein and NSE (Slootweg et al. 1983; Nahrath and Remberger 1986). In keeping with the findings of Slootweg et al. (1983); Zarbo et al. (1983); Goerke et al. (1986); Nahrath and Remberger (1986), we could demonstrate that the granular cell tumour distinguishes itself from the congenital epulis by showing a constant expression of S-100 protein and vimentin and variable expression of NSE. The immunohistochemical findings do not support the assumption of Hoke and Harrelson (1967), that both granular cell ameloblastoma and congenital epulis derive from ameloblast and thus are of the same origin. In keeping with the morphological picture we were able to demonstrate the expression of cytokeratin in the granular cell ameloblastoma. Slootweg et al. (1983) and De Wilde et al. (1984) obtained identical results in their studies. However, the granular cells of the congenital epulis show no expression of cytokeratin (Slootweg et al. 1983; Nahrath and Remberger 1986). Taking the other morphological and immunohistochemical findings into account, the stem cell of the congenital epulis is most probably a fibroblast and not an ameloblast.

The "granular cell ameloblastic fibroma" is a very rare tumour (Couch et al. 1962; Waldron et al. 1963). The name of the tumour has been criticized by White et al. (1978) and Vincent et al. (1987). To our knowledge the immunohistochemical findings are few to date and are limited to the demonstration of cytokeratin in the odontogenic epithelial complexes (Vincent et al. 1987). The tumour in our study showed positive staining for cytokeratin in the epithelial components and vimentin in the granular component, whereas S-100 protein, desmin, neurofilament and NSE showed no positive staining at all. The immunohistochemical findings thus distinguish it from the granular cell tumour (granular cell myoblastoma). We interpret the S-100 protein positive cells lying individually in the granular cell ameloblastoma and in the

"granular cell ameloblastic fibroma" as Langerhans-cells, which also have been found in carcinoma of the oral cavity by Kurihara and Hashimoto (1985). We believe that the cell of origin in the tumor we have studied is a fibroblast of the odontogenic mesenchyma. Table 2 gives an overview of the immunohistochemical findings in the various granular cell tumours of the oral cavity and the jaws. As already mentioned above, the histogenesis of the "granular cell amelolastic fibroma" is controversial. The tumour we have presented here contained areas which are identical with a central odontogenic fibroma (Gardner 1980; Dahl et al. 1981). Figures 1c and 1d document the morphological picture of the odontogenic fibroma and its directly continuous transition into the granular cellular areas of the tumour. There is no doubt that the tumour we have described here is an odontogenic fibroma exhibiting granular cell transformation and not a "granular cell ameloblastic fibroma". The name "granular cell ameloblastic fibroma" (Couch et al. 1962; Waldron et al. 1963; Takeda 1986) is not justified for all of these tumours. Vincent et al. (1987) have suggested that they should be called "central odontogenic fibroma, granular cell variant". Although this name would apply to our tumour the name allows the interpretation that all such lesions arise from odontogenic fibromas. In our opinion such a conclusion would be misleading. We believe that the granular cell-like transformation takes place in the fibroblasts of the odontogenic mesenchyma. At least the theoretical possibility of a granular cell-like transformation taking place in the mesenchymal component of the ameloblastic fibroma can not be ruled out. The name "central granular cell-tumour of the jaws" (White et al. 1978) leaves the question of histogenesis open. Such a name might lead to the false conclusion that this tumour is a rare site for the granular cell tumour (granular cell myoblastoma). Apart from the presence of odontogenic epithelial complexes, the immunohistochemical findings presented clearly demonstrate that both tumours differ in their histogenesis. In our opinion the central granular cell tumour is definitely of odontogenic origin and the name "central granular cell odontogenic tumour" is adequate.

References

Bauer WH, Bauer JD (1953) The so-called "congenital epulis" Oral Surg 6:1065–1071

Bhaskar SN, Akamine R (1955) Congenital Epulis (Congenital granular cell fibroblastoma) Oral Surg 8:517–523

Buchner A (1973) Granular-cell odontogenic cyst. Oral Surg 36:707–712

Couch RD, Morris EE, Vellios F (1962) Granular cell ameloblastic fibroma. Oral Surg 37:398–404

Custer RP, Fust JA (1952) Congenital epulis. Am J Clin Pathol 22:1044–1053

Dahl EC, Wolfson SH, Haugen JC (1981) Central odontogenic fibroma: review of literature and report of cases. J Oral Surg 39:120–124

De Wilde PCM, Slootweg PJ, Müller H, Kant A, Moesker O, Vooijs P, Ramaekers FCS (1984) Immunocytochemical demonstration of intermediate filaments in a granular cell ameloblastoma. J Oral Surg 13:29–39

Enzinger FM, Weiss SW (1983) Soft tissue tumors. The C.V. Mosby Company. St. Louis, Toronto, London pp 745–753

Gardner DG (1980) The central odontogenic fibroma: An attempt at clarification. Oral Surg 50:425–432

Goerke K, Saldana-Araneta T, Meier D, Gusek W (1986) Granularzelltumor der Mamma. Pathologe 7:294–297

Gold L, Christ T (1970) Granular-cell odontogenic cyst. Oral Surg 29:437–442

Hartman KS (1974) Granular-cell ameloblastoma. Oral Surg 38:241–253

Hoke HF, Harrelson AB (1967) Granular cell ameloblastoma with metastasis to the cervical vertebrae. Cancer 20:991–999

Kameyama Y, Mizohata M, Takehana S, Murata H, Manabe H, Mukai Y (1983) Ultrastructure of the congenital epulis. Virchows Arch [A] 401:251–260

Kameyama Y, Takehana S, Mizohata M, Nonobe K, Hara M, Kawai T, Fukaya M (1987) A clinicopathological study of ameloblastomas. Int J Oral Maxillofac Surg 16:706–712

Kay S, Elzay RP, Willson MA (1971) Ultrastructural observations on a gingival granular cell tumor (congenital epulis) Cancer 27:674–680

Kurihara K, Hashimoto N (1985) The pathological significance of Langerhans cells in oral cancer. J Oral Pathol 14:289–298

Lack EE, Perez-Atayde AR, McGill TJ, Vawter GF (1982) Gingival granular cell tumor of the newborn (congenital "epulis"): ultrastructural observations relating to histogenesis. Hum Pathol 13:686–689

Lifshitz MS, Flotte TJ, Greco MA (1984) Congenital granular cell epulis. Immunohistochemical and ultrastructural observations. Cancer 53:1845–1848

Lownie JF, Altini M, Shear M (1976) Granular cell peripheral odontogenic fibroma. J Oral Surg 5:295–304

Matthews JB, Mason GI (1982) Oral granular cell myoblastoma: an immunohistochemical study. J Oral Pathol 11:343–352

Nasu M, Takagi M, Yamamoto H (1984) Ultrastructural and histochemical studies of granular-cell ameloblastoma. J Oral Pathol 13:448–456

Nathrath WJB, Remberger K (1986) Immunohistochemical study of granular cell tumours. Virchows Arch [A] 408:421–434

Rohrer MD, Young SK (1982) Congenital epulis (gingival granular cell tumor): Ultrastructural evidence of origin from pericytes. Oral Surg 53:56–63

Slootweg P, de Wilde P, Vooijs P. Ramaekers F (1983) Oral granular cell lesions. Virchows Arch [A] 402:35–45

Sunderland FP, Sunderland R, Smith CJ (1983) Granular cells associated with the enamel organ of a developing tooth. J Oral Pathol 12:1–6

Takeda Y (1986) Granular cell ameloblastic fibroma, ultrastructure and histogenesis. Int J Oral Maxillofac Surg 15:190–195

Tandler B, Rossi EP (1977) Granular cell ameloblastoma: electron microscopic observations. J Oral Pathol 6:401–412

Trodahl JN (1972) Ameloblastic fibroma. A survey of cases from the Armed Forces Institute of Pathology. Oral Surg 33:547–558

Vincent SD, Hammond HL, Ellis GL, Juhlin JP (1987) Central granular cell odontogenic fibroma. Oral Surg 63:715–721

Waldron CA, Thompson CW, Conner WA (1963) Granular-cell ameloblastic fibroma. Oral Surg 16:1202–1213

White DK, Chen S-Y, Hartman KS, Miller AS, Gomez LF (1978) Central granular-cell tumor of the jaws (the so-called granular-cell ameloblastic fibroma). Oral Surg 45:396–405

Zarbo RJ, Lloyd RV, Beals TF, McClatchey KD (1983) Congenital gingival granular cell tumor with smooth muscle cytodifferentiation. Oral Surg 56:512–520

Received March 7, 1989 / Accepted June 15, 1989