

CASE REPORT

Granular Cell Variant of Atypical Fibroxanthoma

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We report a case of atypical fibroxanthoma of the ear in which the dominant part of the tumor has granular cell appearance. Areas identical to conventional atypical fibroxanthoma were present only at the lateral infiltrating borders. Histologically the granular cells resembled those of the classical granular cell tumors but exhibited significant pleomorphism and a high mitotic rate. Immunostains

for vimentin, CD68 and NK1/C3 were positive but for S-100, HMB-45, myogenic and epithelial markers were negative. The predominance of the granular cells in an atypical fibroxanthoma supports the concept that a small subset of tumors with granular cell phenotype are of nonneural origin. (Pathology Oncology Research Vol 2, No 4, 244-247, 1996)

Key words: fibrohistiocytic tumors, granular cells, atypical fibroxanthoma

Introduction

The name "myoblast myoma" that appeared in the Abrikosoff's original article¹ suggests the myogenic origin of granular cells. In the last few decades the results of both ultrastructural and immunohistochemical studies supported the neural origin of most granular cell tumors.^{3,5,7,8,16} However, granular cells have been observed in numerous different neoplastic lesions^{2,3,10,11,13, 14,17} and in reactive processes.^{6,20}

Recently a series of smooth muscle tumors with a granular cell change,^{7,8} and a granular cell variant of dermatofibrosarcoma protuberans (DFSP)² have been reported. LeBoit et al¹⁵ described four cases of unique cutaneous tumors which they named 'primitive polypoid granular cell tumor' (PPGT).

We report an atypical fibroxanthoma of the skin in which the tumor cells displayed extensive granular cell transformation. We believe this to be the first report of such a variant. The occurrence of the 'granular cell phenomenon' in an atypical fibrosarcoma supported the concept that granular cell tumors are not a homogenous group in differentiation.

Material and methods

The surgical specimen was fixed in 10% buffered formalin and processed by standard technique to paraffin wax. Sections 5 µm thick were stained with hematoxylin and eosin, periodic acid Schiff with and without diastase digestion and Gomori's reticulin stains. Parts of the formalin fixed material were postfixed in 2% glutaraldehyde and 2% osmium tetroxide, and embedded in araldite. Ultrathin sections were stained with lead citrate and uranyl acetate. For immunohistochemical examination deparaffinized tissue sections were stained with a panel of mono- and polyclonal antibodies using the avidin-biotin-peroxidase method. The reagents, their sources, and the results are summarized in *Table 1*.

Report of the case

An 82 year old man was admitted with a dome-shaped ulcerated skin tumor on the right ear that he had noticed several months prior to admission. The tumor was excised in toto.

Pathological examination

Gross Findings The specimen measured 3 x 2 cm skin with cartilage on the base. In the center, the protuberated tumor measured 1.5 cm in diameter. The tumor did not

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Table 1. Immunohistochemical reactions and results in the study of granular cell variant of atypical fibroxanthoma

Antibody	Source	Granular cells	Spindle cells
Cytokeratin (lu-5)	BioGenex	neg	neg
EMA	BioGenex	neg	neg
Vimentin	Dako	weak pos	pos
Desmin	Dako	neg	neg
Smooth muscle actin (1A4)	Dako	neg	neg
S-100*	Dako	neg	neg
NSF	Dako	weak pos	neg
α -1-antitrypsin	BioGenex	weak pos	weak pos
MAC 387	Dako	neg	neg
CD68 (KP1)	Dako	pos	pos
HMB-45	Dako	neg	neg
NK1/C3	BioGenex	pos	neg
CD43	Dako	neg	neg
Factor VIIIa*	BioGenex	neg	neg

* Polyclonal antibodies, all the others are monoclonal. EMA epithelial membrane antigen, neg - negativity; pos - positivity

attach to the cartilage. On the cut surface, the lesion was firm, grayish-white focally with hemorrhage.

Microscopy - Histologically the epidermis was ulcerated and the surface was covered by red blood cells. The thickness of the tumor under the microscope was 12 mm. The neoplasm extended to the deep reticular dermis, and at its base it had an expansive rather than infiltrative border. Laterally the tumor cells infiltrated the preexisting collagen of the dermis. In the superficial region of the tumor dilated capillaries were seen (*Fig.1*). The center of the tumor was characterized by polygonal or slightly elongated cells in a sheet-like pattern. The cytoplasm was filled with abundant eosinophilic granules (*Fig.2*). This granular cell area accounted for approximately 90% of the

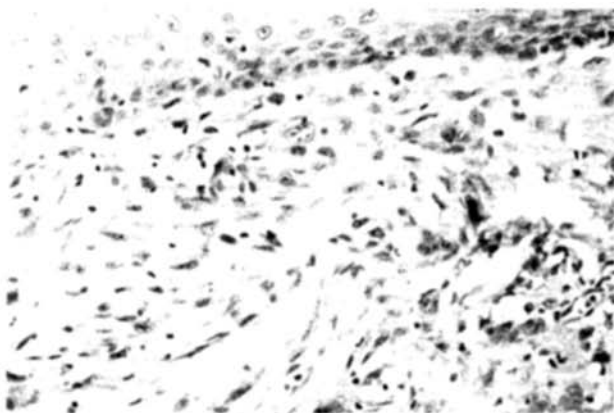


Figure 1. Dilated capillaries in the tumor mass beneath the epidermis

tumor. The nuclei were pale, exhibited pleomorphism and contained prominent eosinophilic nucleoli. The nuclear membranes were well defined, but bizarre, multinucleated and hyperchromatic forms were also noted. Mitoses, many with abnormal appearance, were frequent (3-4/HPF). The granules were PAS positive and diastase resistant. At margins, where the tumor infiltrated the collagen fibers the granular cells were gradually intermingled with spindle cells (*Fig.3*). These spindle cells were arranged in a vague fascicular, or even in storiform pattern (*Fig.4*), and exhibited similar nuclear characteristics as seen in the granular cells.

Immunohistochemistry - The results are summarized in *Table 1*. The granular and spindle cells showed immunoreactivity for vimentin and CD68 (*Fig.5*), but the former was weaker in the granular cells. Both cell types showed weak positive staining for α -1-antitrypsin. The granular cells were strongly positive with NK1/C3 (*Fig.6*), and focally positive for neurone specific enolase (NSE), while

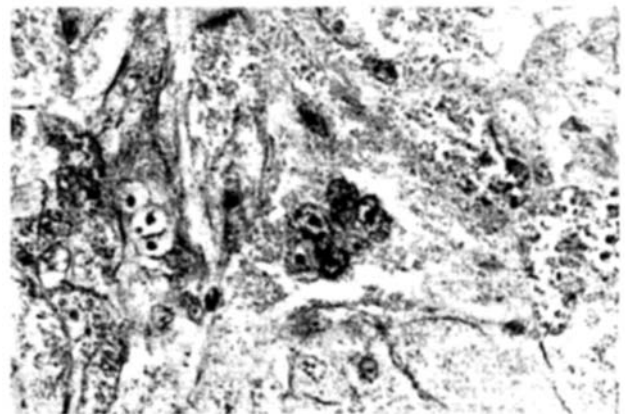


Figure 2. Polygonal cells with markedly granular cytoplasm. Note the prominent nucleoli.

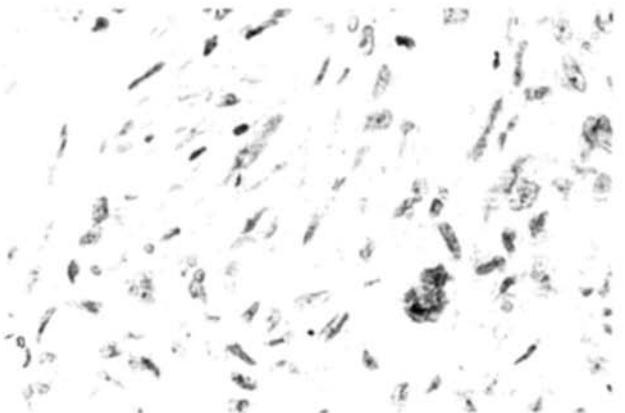


Figure 3. Admixture of polygonal and spindle cells. Nuclei show significant pleomorphism.

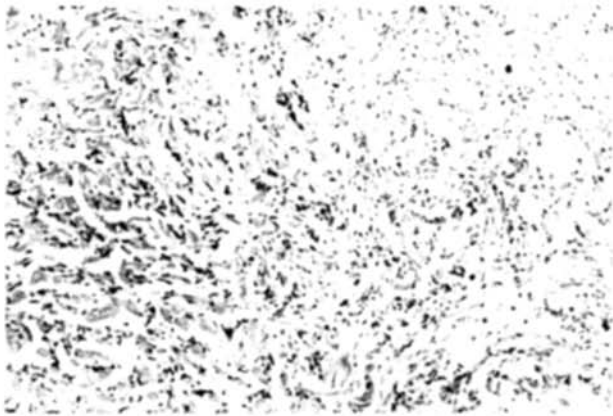


Figure 4. Storiform and fascicular pattern at the periphery of the tumor.



Figure 6. Variable CD68 positivity in granular cells.

the spindle cells were negative. Both cell types were negative for all the other markers examined.

Ultrastructure – Only granular cell areas were included in the blocks examined. Although preservation was suboptimal, the cytoplasmic granules showed close similarity to other granular cell tumors (Fig.7). A small number of short channels in the rough endoplasmic reticulum were observed, but no external lamina, non-myelinated axons, microtubules, angulate bodies, myofilaments or melanosomes were present.

Discussion

We have designated the above described tumor as a granular cell atypical fibroxanthoma. It is well known that granular cells may be present focally or even in large areas in reactive processes^{6,21} and in different mesenchymal,^{2,7,11,14,17,18,20,23} bone,²² central nervous system,^{19,24} and epithelial tumors.^{4,10,25} To our knowledge, there has been no previous report of this granular cell variant of atypical fibroxanthoma. Therefore it is essential that the diagnosis be justified in detail.

Atypical fibroxanthoma occurs in two clinical settings.⁴ Our case represents the more common form of the disease, in which the lesion develops as a solitary bleeding nodule in the head and neck region of elderly patients. In our case it was located on the ear and the bleeding was originated from the dilated capillaries beneath the surface. The appearance of the infiltrating atypical spindle cells at the periphery, and their arrangement into fascicular and storiform patterns suggested their fibrohistiocytic origin. The significant pleomorphism and the high mitotic activity must be considered as signs of malignancy. Both granular and spindle cells were positive with CD68 and vimentin, suggesting histiocytic differentiation. Based on the immunohistochemical negativity for epithelial markers and the ultrastructural absence of epithelial components the epithelial origin could be excluded. There were no signs of melanocytic differentiation either immunohistochemically or ultrastructurally. The weak response to NSE in the granular cells does not rule out the diagnosis of atypical fibroxanthoma as it is commonly present in all types of granular cell tumors.⁵ The positive NSE

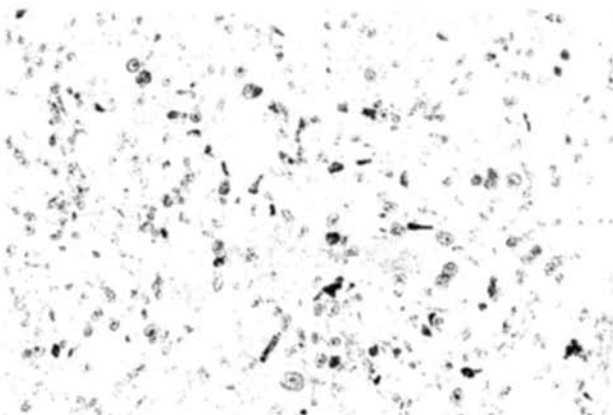


Figure 5. NK1/C3 positivity in granular cells.

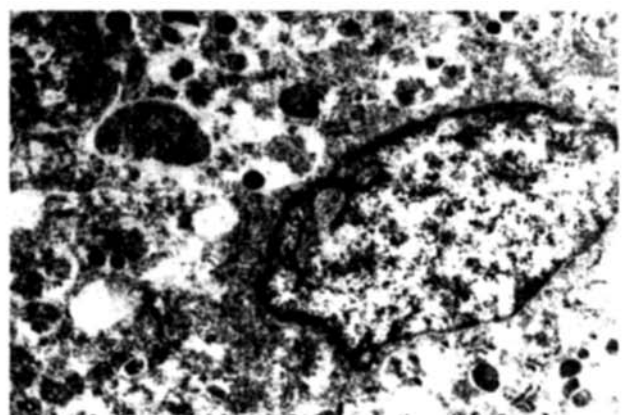


Figure 7. Ultrastructural cytoplasmic granules show similarity to the other types of granular cell tumors.

reaction is not specific for neuroendocrine differentiation.¹² Apparently, the positive reaction to NK1/C3 is surprising, as this monoclonal antibody was originally developed for melanoma-associated antigen. However, a strong positive reaction with NK1/C3 in atypical fibroxanthoma and DFSP has been reported.¹⁵ The positivity is probably due to a cross reaction. In our case the localization, the nuclear structure, the protuberant growth pattern and the negativity for S-100 protein excluded the diagnosis of neural granular cell tumor also named classical Abrikossoff tumor. Generally in malignant Abrikossoff tumor there is only moderate polymorphism and low mitotic activity, while the immunohistochemical reaction against S-100 protein is positive.⁷

In 1991 Banerjee et al² documented two cases of a granular cell variant of DFSP, and LeBoit et al¹³ described four lesions, which they named "primitive polypoid granular cell tumor" (PPGT). The granular cell variant of DFSP contained typical spindle cell areas with a storiform pattern, and immunohistochemically was characterized by the negative response to S-100, myelin basic protein, NSE, α -1-antichymotrypsin, and MAC 387, while it was positive for NK1/C3 in the granular cell areas. The mitotic activity was not mentioned. The CD68 reaction was not performed. LeBoit proposed the PPGT designation for their cutaneous granular cell tumors,¹³ but it must be mentioned, that detailed immunohistochemical and ultrastructural examination was performed only in two cases. The "primitive" term is not quite appropriate as it refers only to the poor immunohistochemical findings. Besides, in one case α -1-antichymotrypsin was observed, and in another case, weak FXIIIa expression was described so the possibility of fibrohistiocytic origin might be raised. The follow-up data also contradict this term, because neither metastases nor recidivas were observed.

We suggest, that our case shows a histogenetic association with both granular cell variants of DFSP, and with the PPGT. DFST, on the basis of less pleomorphic appearance and characteristic storiform pattern can be considered as a more differentiated variant, while it seems that in PPGT the granular cells overgrew the original, probably fibrohistiocytic derived lesion. Our results support the concept that granular cell phenotype in a tumor is not equal to neural differentiation. Granular cell tumors in atypical localization or with any non-conventional histological sign should be examined in detail, and the application of a wide-range immunohistochemical panel is recommended.

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