

Granular cell atypical fibroxanthoma

Abstract: We report on two patients with granular cell atypical fibroxanthoma. Both neoplasms were solitary, light-tan, dome-shaped papules on sun-exposed areas of the head in two elderly white men. Microscopically, these neoplasms showed a dermal proliferation of pleomorphic granular cells with irregular hyperchromatic nuclei, multinucleated cells, and scattered mitoses. Immunohistochemical stains were positive for CD68 and vimentin and negative for Melan-A or human melanoma black (HMB)-45, S-100 protein, pancytokeratin, and actin, consistent with atypical fibroxanthoma. The differential diagnosis of granular cells in neoplasms containing cytological pleomorphism is challenging in view of the many different neoplasms that may present with granular cytoplasm. These include the conventional granular cell tumor and its malignant form, leiomyoma, leiomyosarcoma, dermatofibroma, dermatofibrosarcoma protuberans, and angiosarcoma.

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Helwig¹ described atypical fibroxanthoma in 1961. Since that seminal article, several variants were identified and included atypical fibroxanthomas with spindle cells, pigmented cells, clear cells, pleomorphic cells, multinucleated giant cells, aneurysmal zones, and myxoid areas.^{2–5} In 1996, Orosz^{6,7} reported on a single case with granular cell cytoplasm. Presented here are two additional examples of this rare type of atypical fibroxanthoma.

Case reports

The first patient was an 81-year-old white man with a 0.65 × 0.55-cm dome-shaped, light-tan, keratotic papule on the right preauricular area. An excision was performed. The patient was seen 1 week later for follow up and has not returned with further complaints.

The second patient, a 77-year-old white man, presented with multiple, rough, scaly areas clinically consistent with actinic keratoses and a 0.8 × 0.7-cm shiny, dome-shaped, light-tan nodule on the scalp. A shave biopsy of it was done. One week following the biopsy, Mohs' surgery was performed, and the lesion was cleared after three stages. The patient was followed at regular intervals, and the neoplasm has not reappeared either from persistence or from metastasis.

Pathological findings

Histologically, both cases had similar features. At scanning magnification, the neoplasms were found to be expansile dermal nodules of mostly mononuclear cells. (Fig. 1A). The overlying epidermis was atrophic in one case (Fig. 2A) and acanthotic in the other (Fig. 1A). Most of the neoplasms were composed of pleomorphic mononuclear cells with ample, homogeneous, eosinophilic cytoplasm. The cytoplasm was filled with finely dispersed and clumped eosinophilic granules. Many of the cells were relatively uniform and monomorphous (Fig. 2A). Focally, the cells contained pleomorphic nuclei, whether the cells were mononuclear or multinuclear. Scattered mitotic figures, some of which were abnormal, were also identified (Figs 1B and 2B). Solar elastosis was present peripheral to and below the neoplasms. Vimentin and CD68 were positive, strongly and diffusely, in the cytoplasm (Fig. 2C), while Melan-A or HMB-45, S-100, pancytokeratin, and actin were all negative.

Discussion

Granular cells are identified rarely in a variety of neoplastic and non-neoplastic proliferations. Both benign and malignant neoplasms present within the dermis can show such differentiation; these neoplasms

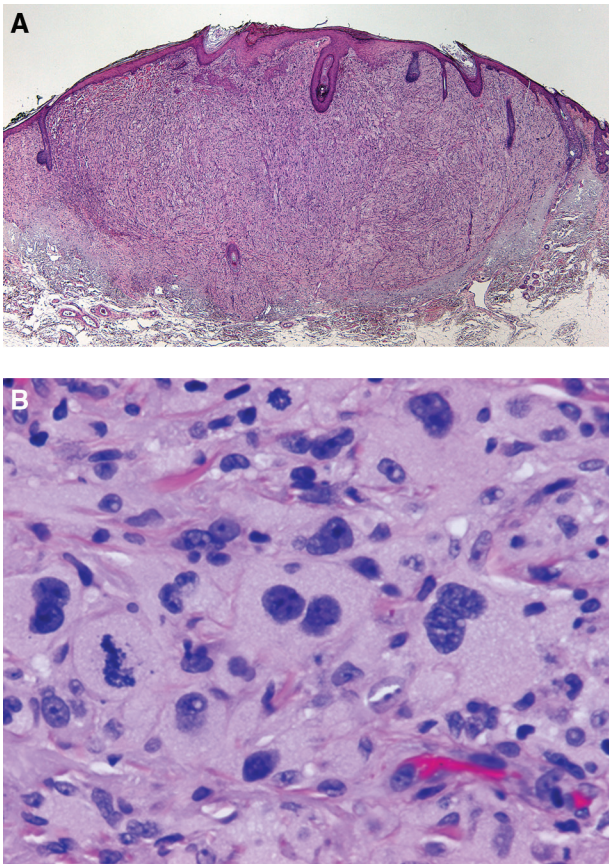


Fig. 1. Case 1: (A) This scanning magnification of the neoplasm shows a diffuse proliferation of cells surrounded by solar elastosis and surfaced by epidermal hyperplasia. (B) At high magnification, the cells are found to be not only granular uniformly, but their nuclei are obviously pleomorphic, including two that show mitotic figures.

include leiomyoma, schwannoma, dermatofibroma, angiosarcoma, leiomyosarcoma, basal cell carcinoma, dermatofibrosarcoma protruberans, atypical fibroxanthoma,^{6,7,8-21} and the classical granular cell tumor, including its rare malignant analog. Immunoperoxidase studies are often necessary in the evaluation of tumor phenotype because of the similarities of some of the neoplasms.

Atypical fibroxanthomas are cytologically pleomorphic epithelioid and spindle cell neoplasms regarded commonly as a superficial variant of malignant fibrous histiocytoma.²² It is well known that these neoplasms present as solitary lesions and are located commonly in sun-damaged skin of the head or neck of elderly patients.^{1,22,23}

Clinically, the neoplasm often grows rapidly and appears as a tan to light-brown, dome-shaped nodule usually less than 2 cm in diameter; ulceration is common.^{1,22,23} Microscopically, it consists of a dermal proliferation of bizarre pleomorphic spindle-shaped and epithelioid cells and scattered multinucleated giant tumor cells.^{1,22,23} The nuclei are hyperchromatic

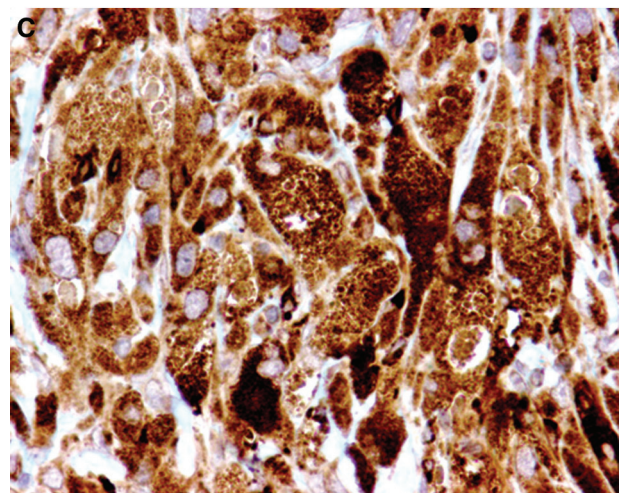
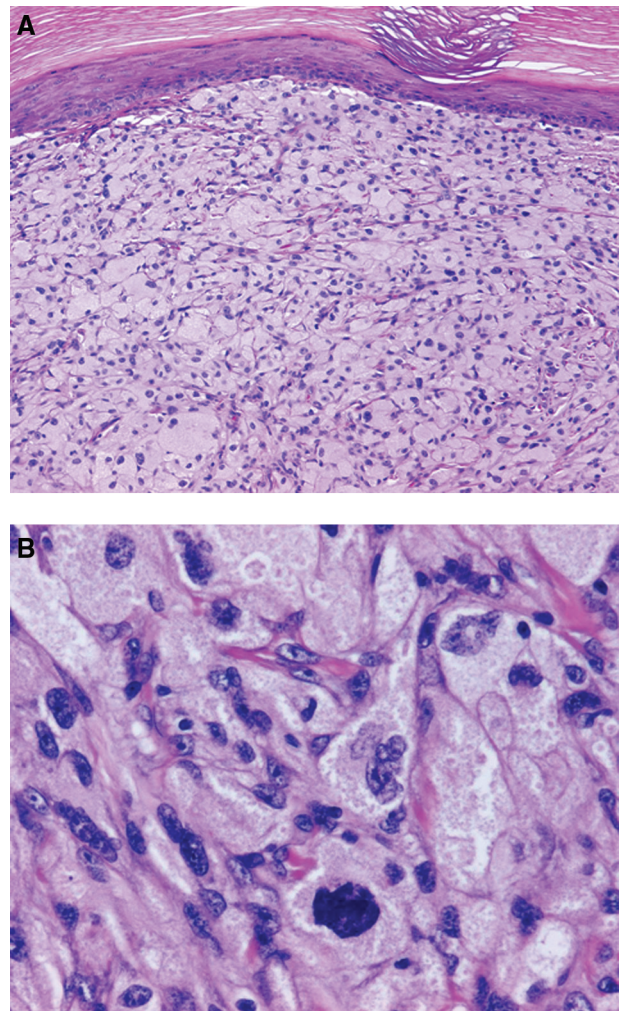


Fig. 2. Case 2: (A) At low magnification, this neoplasm is found to harbor less nuclear pleomorphism than does the neoplasm in Case 1. (B) Other areas of the same neoplasm show similar cytoplasmic features, but the nuclei are pleomorphic and have uneven nuclear contours. Note the prominent exploded mitosis in the lower part of the figure. (C) CD68 marks strongly the cytoplasm of all of the neoplastic cells.

and multilobulated. Conventional and unconventional mitotic figures are identified easily. These neoplasms often are difficult to differentiate from other malignant neoplasms; therefore, immunostains are performed usually to help establish the diagnosis. It is well known that atypical fibroxanthomas are positive for macrophagic markers and generally negative for epithelial, melanocytic, neural, and other mesenchymal markers.^{24,23}

Since Helwig's¹ original description of atypical fibroxanthoma in 1961, several cytological variants were identified²⁻⁷ including a single case of the granular cell variant of atypical fibroxanthoma reported by Orosz in 1996.^{6,7} The two additional examples of it that we present have the clinical (Table 1) and histopathological findings characteristic of atypical fibroxanthoma.

LeBoit and co-workers have described morphologically similar neoplasms that they named as 'primitive polypoid granular cell tumors'. The four patients described had somewhat variable clinical presentations but shared a primitive immunophenotype, particularly the negativity for S-100 protein. The fourth case has the typical clinical presentation for atypical fibroxanthoma. We are uncertain of the nature of these neoplasms, and because the authors did not consider the diagnosis of atypical fibroxanthoma, we have chosen not to include them in our table. It is very possible that their fourth case represented an atypical fibroxanthoma.²⁵

The cytological pleomorphism and abundance of granular cells in granular cell atypical fibroxanthoma are similar to that of the malignant analog of granular cell tumor. Differentiation histologically of these two neoplasms is challenging and can be achieved by immunohistochemistry. The granular cells of malignant granular cell tumor are diffusely positive for S-100,

while those of granular cell atypical fibroxanthoma are uniformly negative, allowing for a distinction between the two neoplasms. At times, there are many S-100-positive dendritic cells in atypical fibroxanthomas contrasting with the negative tumor cells.

Table 2 summarizes an expanded differential diagnosis of dermal neoplasms with granular cell changes along with the expected antibody-staining patterns and cytological features used in establishing a diagnosis. While variable positivity with actin²⁴ and factor XIIIa²⁴ is reported in the literature in atypical fibroxanthoma, these stains were negative in the three cases of granular cell variant.

Tumor architecture, cell cytology, and immunophenotype are used to identify the many variants of atypical fibroxanthoma. While a small number are more aggressive, accurate diagnosis of these tumors is important given their uniformly excellent prognosis when excised completely.^{22,23}

References

1. Helwig EB. Atypical fibroxanthoma. Proceedings of 18th Annual Tumor Seminar San Antonio Society of Pathologists, 1961. *Tex State J Med* 1963; 59: 664.
2. Crowson AN, Carlson-Sweet K, et al. Clear cell atypical fibroxanthoma: a clinicopathologic study. *J Cutan Pathol* 2002; 29 (6): 374.
3. Khan ZM, Cockerell CJ. Atypical fibroxanthoma with osteoclast-like multinucleated giant cells. *Am J Dermatopathol* 1997; 19: 174.
4. Diaz-Cascajo C, Borghi S, Bonckowitz M. Pigmented atypical fibroxanthoma. *Histopathology* 1998; 33: 537.
5. Silvis NG, Swanson PE, Manivel JC, Kaye VN, Wick MR. Spindle-cell and pleomorphic neoplasms of the skin. A clinicopathological and immunohistochemical study of 30 cases, with emphasis on atypical fibroxanthomas. *Am J Dermatopathol* 1988; 10: 9.
6. Orosz Z, Kelemen J, Szentirmay Z. Granular cell variant of atypical fibroxanthoma. *Pathol Oncol Res* 1996; 2: 244.
7. Orosz Z. Atypical fibroxanthoma with granular cells. *Histopathology* 1998; 33 (1): 88.
8. Hitchcock MG, Hurt MA, Santa Cruz DJ. Cutaneous granular cell angiosarcoma. *J Cutan Pathol* 1994; 21 (3): 256.
9. Banerjee SS, Harris M, Hamid BNA. Granular cell variant of dermatofibrosarcoma protuberans. *Histopathology* 1990; 17: 375.

Table 1. Case reports, including the ones presented in this article

| Case | Age (years) | Sex | Location |
|--------|-------------|------|--------------------|
| Orosz | 82 | Male | Right ear |
| Case 1 | 81 | Male | Right preauricular |
| Case 2 | 77 | Male | Scalp |

Table 2. Neoplasms exhibiting granular cell changes

| Diagnostic criteria | Granular cell tumor | Malignant granular cell tumor | Dermatofibroma | DFSP | Leiomyoma | Leiomyosarcoma | Angiosarcoma | AFX |
|---------------------|---------------------|-------------------------------|----------------|----------|-----------|----------------|--------------|----------|
| Pleomorphism | Absent | Present | Absent | Absent | Absent | Present | Present | Present |
| Mitoses | Absent | Present | Absent | Variable | Absent | Present | Present | Present |
| CD68 | Positive | Positive | Positive | Positive | Positive | Positive | Positive | Positive |
| S-100 | Positive | Positive | Negative | Negative | Negative | Negative | Negative | Negative |
| CD34 | Negative | Negative | Variable | Positive | Negative | Negative | Positive | Negative |
| Factor XIIIa | Negative | Negative | Positive | Variable | Negative | Negative | Negative | Negative |
| Actin | Negative | Negative | Positive | Negative | Positive | Positive | Negative | Negative |
| CD31 | Negative | Negative | Negative | Negative | Negative | Negative | Positive | Negative |
| Melan-A | Negative | Negative | Negative | Negative | Negative | Negative | Negative | Negative |

DFSP, dermatofibrosarcoma protuberans; AFX, atypical fibroxanthoma.

10. Maire G, Pedeutour F, Coindre JM. COLIA-PDGFB gene fusion demonstrates a common histogenetic origin for dermatofibrosarcoma protuberans and its granular cell variant. *Am J Surg Pathol* 2002; 26 (7): 932.
11. Barr RJ, Graham JH. Granular cell basal cell carcinoma. *Arch Dermatol* 1979; 115: 1064.
12. McWilliam LJ, Harris M. Granular cell angiosarcoma of the skin: histology, electron microscopy, immunohistochemistry of a newly recognized tumor. *Histopathology* 1985; 9: 1205.
13. Mentzel T, Wadden C, Fletcher CD. Granular cell change in smooth muscle tumors of the skin and soft tissue. *Histopathology* 1994; 24: 223.
14. Nistal M, Paniaque R, Picazo ML, et al. Granular changes in vascular leiomyosarcoma. *Virchows Arch A Pathol Anat Histopathol* 1980; 386: 239.
15. Suster S, Rosen LB, Sanchez JC. Granular cell leiomyosarcoma. *Am J Dermatopathol* 1988; 10: 234.
16. Sironi M, Assi A, Pasquinelli G, Cenacchi G. Not all granular cell tumors show schwann cell differentiation: a granular cell leiomyosarcoma of the thumb, a case report. *Am J Dermatopathol* 1999; 21 (3): 307.
17. Pour P, Althoff J, Cardesa A. Granular cells in tumors and in nontumorous tissue. *Arch Pathol Lab Med* 1973; 95: 135.
18. Shimokama T, Watanabe T. Leiomyoma exhibiting a marked granular change: granular cell leiomyoma vs. granular cell schwannoma. *Hum Pathol* 1992; 23: 327.
19. Sanz-Trelles A, Weil-Lara B, Acedo-Rodriguez C. Dermatofibroma with granular cells. *Histopathology* 1997; 30: 495.
20. Zelger BG, Steiner H, Kutzner H, Rulten A, Zelger B. Granular cell dermatofibroma. *Histopathology* 1997; 31 (3): 258.
21. LeBoit PE, Barr RJ. Unusual mesenchymal proliferations associated with dermatofibromas. *J Cutan Pathol* 1991; 18: 376.
22. Enzinger FM, Weiss SW. *Soft tissue tumors*. St Louis: Mosby, 2001; 536.
23. Fretzin DF, Helwig EB. Atypical fibroxanthoma of the skin. A clinicopathologic study of 140 cases. *Cancer* 1973; 31: 1541.
24. Longacre TA, Smoller BR, Rouse RV. Atypical fibroxanthoma. Multiple immunohistologic profiles. *Am J Surg Pathol* 1993; 17: 1199.
25. LeBoit PE, Barr RJ, Burall S, Metcalf JS, Yen TSB, Wick MR. Primitive polypoid granular-cell tumor and other cutaneous granular-cell neoplasms of apparent nonneural origin. *Am J Surg Pathol* 1991; 15 (1): 48.