

Granular cell variant of atypical fibroxanthoma. A case report

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SUMMARY

We report a case of an 84-year old female with granular cell atypical fibroxanthoma. The patient had an exophytic cutaneous tumor without ulceration localized on the left thigh. Histologically, the tumor consisted of a large epithelioid and spindle cells with a moderate to abundant amount of eosinophilic granular cytoplasm. The nuclei were irregular with coarse chromatin and some exhibited prominent nucleoli. Some of the tumor cells displayed atypical bizarre pleomorphic nuclei. Mitotic figures were sparse. Immunohistochemically, the tumor cells showed diffuse positivity for vimentin, CD10, NKi/C3 and CD68 (KP1). CD68 (PGM1) was positive only focally. Other markers examined, which included Melan A, HMB45, S-100 protein, cytokeratin AE1/AE3, desmin, h-caldesmon, α -smooth muscle actin, NSE, CD1a, CD34, and CD31 were negative. A granular cell variant of atypical fibroxanthoma is rare, and only a few cases have been reported in the literature to date.

Keywords: dermal tumor – atypical fibroxanthoma – granular cells – cytoplasmic granules – granular cell tumors

Granular cell varianta atypického fibroxantomu. Popis případu

SOUHRN

Prezentujeme případ 84 leté ženy s granulární variantou atypického fibrózního fibroxantomu. Pacientka měla na levém stehně exofytický kožní nádor bez ulcerace. Mikroskopicky byl nádor tvořený velkými epitelioidními a vřetenitými buňkami se středním a velkým množstvím eosinofilní granulované cytoplazmy. Jádra byla nepravidelná s hrubým chromatinem a někde se zřetelnými jádérky. Některé buňky měly bizarním pleomorfní jádra. Mitózy byly zastíženy pouze řídce. Imunohistochemicky byl v nádorových buňkách pozitivní průkaz vimentinu, CD10, Nki/C3 a CD68 (KP1). CD68 (PGM1) byl pozitivní pouze fokálně. Další markery včetně Melanu A, HMB45, S-100 proteinu, cytokeratinů AE1/AE3, desminu, h-caldesmonu, α -hladkosvalového aktinu, NSE, CD1a, CD34 a CD31 byly negativní. Granulární varianta atypického fibrózního fibroxantomu je vzácná, dosud bylo v literatuře prezentováno pouze několik případů.

Klíčová slova: kožní nádor – atypický fibroxantom – granulární buňky – cytoplasmatická granula – nádory z granulárních buněk

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Atypical fibroxanthoma (AFX) is a dermal tumor with a favorable prognosis, which is commonly regarded as a superficial variant of malignant fibrous histiocytoma (1,2). AFX is usually present as a solitary lesion on the sun-damaged skin of older adults. Cases associated with xeroderma pigmentosum and immunosuppression have been reported, and ultraviolet-induced p53 mutations have been identified in these lesions (3,4). AFXs exhibit highly pleomorphic histologic features, however the metastatic potential is low. Several morphological subtypes have been described including a clear-cell, desmoplastic or keloidal, angiomatoid, hemosiderotic, myxoid, and rare case reports of the granular cell variant (4-9).

MATERIALS AND METHODS

Sections from formalin-fixed, paraffin-embedded tissue blocks were stained with hematoxylin-eosin. Selected sections were analyzed immunohistochemically using the avidin-biotin complex method with antibodies directed against the following antigens: vimentin (1:300, Bio-Genex, San Ramon, CA, USA), cytokeratin AE1/AE3 (1:50, Dako, Glostrup, Denmark), CD10 (1:100, NeoMarkers, Fremont), desmin (1:200, Dako), S-100 protein (1:1600, Dako), α -smooth muscle actin (1:100, Dako), h-caldesmon (1:50, Dako), HMB-45 (1:50, Dako), CD1a (1:30, Dako), NSE (1:400, Dako), CD34 (1:50, Dako), CD31 (1:50, Dako), melan A (1:25, Novocastra), NKi/C3 (1:100 Bio, Genex), CD68 (KP1) (1:25, Dako), and CD68 (PGM1) (1:25, Dako).

Electron microscopy examination was done on formalin-fixed, paraffin-embedded tissue, because glutaraldehyde-fixed material was not available.

RESULTS

The excisional cutaneous biopsy from the left thigh of an 84-year old female measured 27 x 14 x 5 mm. In the center of the skin excision was a non-ulcerated exophytic tumor 10 x 10 x 5 mm.

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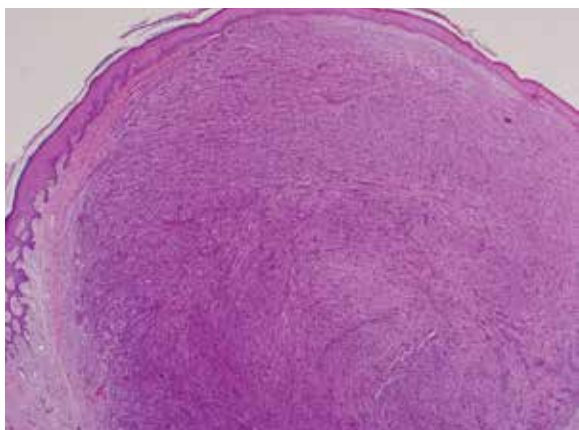


Fig. 1. Low power view showing sharp demarcation of the tumor from surrounding tissue (H&E, original magnification 20x).

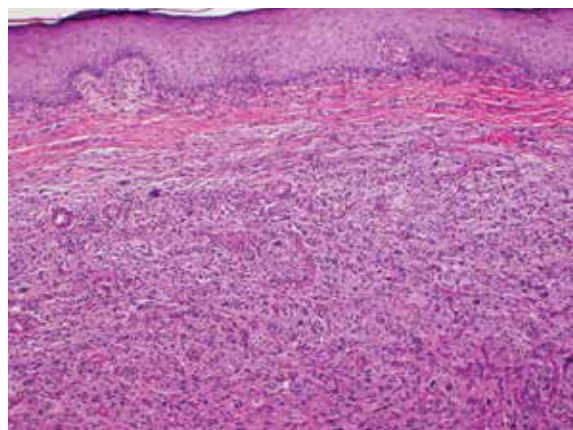


Fig. 2. AFX shows a proliferation of large epithelioid and spindle cells have haphazardly infiltrated the dermis (H&E, original magnification 100x).

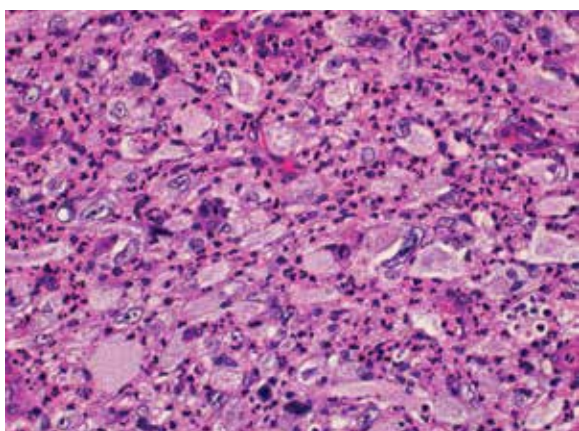


Fig. 3. Tumor cells have a moderate to abundant amount of eosinophilic granular cytoplasm. The nuclei are irregular and some exhibits prominent nucleoli (H&E, original magnification 400x).

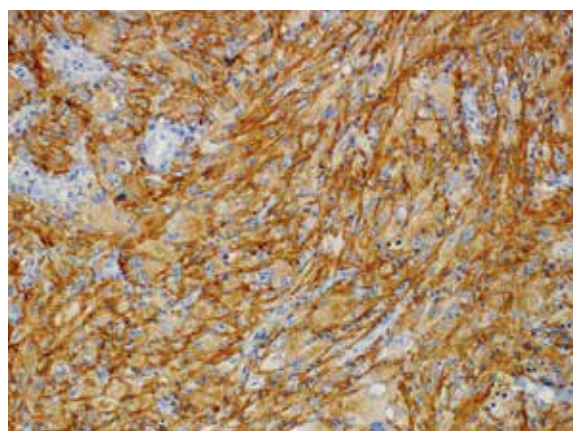


Fig. 4. Immunohistochemical expression of CD10 in tumor cells (original magnification 200x).

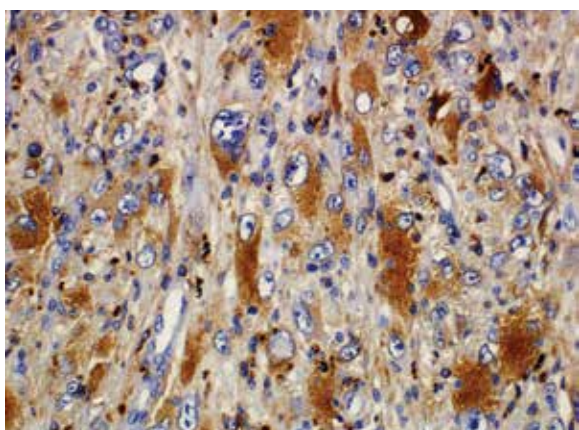


Fig. 5. Immunohistochemical expression of CD68 (KP1) in tumor cells (original magnification 400x).

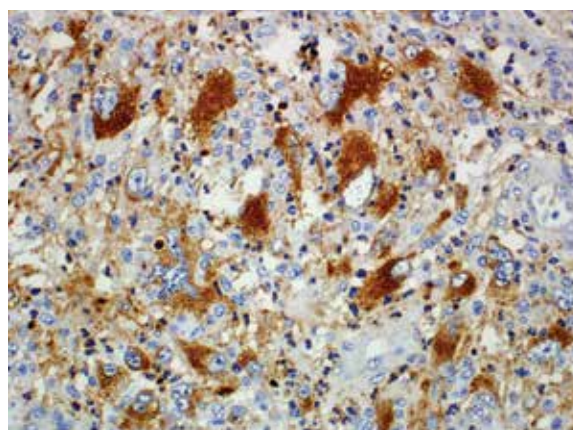


Fig. 6. Strong cytoplasmic immunohistochemical expression of NKi/C3 in tumor cells (original magnification 400x).

Histologically, the tumor consisted of a large epithelioid and spindle cells with a moderate to abundant amount of eosinophilic granular cytoplasm (Fig. 1,2). The nuclei were irregular with coarse chromatin and some exhibited prominent nucleoli. Some of the tumor cells displayed atypical bizarre pleomorphic nuclei (Fig. 3). Mitotic figures were rare up to 3/10 HPF. The tumor

cells haphazardly infiltrated the dermis, focally in a vague storiform pattern. Immunohistochemically, the tumor cells showed diffuse positivity for vimentin, CD10, NKi/C3, and CD68 (KP1) (Fig. 4-6). CD68 (PGM1) was positive only focally. Other markers examined were negative, including Melan A, HMB45, S-100 protein, cytokeratin AE1/AE3, desmin, h-caldesmon, α -smooth

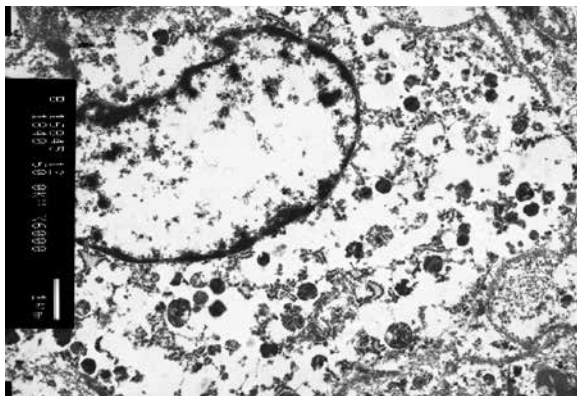


Fig. 7. Electron micrograph showing prominent electron-dense cytoplasmic granules and margination of nuclear chromatin in tumor cell.

muscle actin, CD34, and CD31. Only scattered non-tumorous dendritic cells in the interstitium were positive for S-100 protein and CD1a. There were scattered inflammatory cells, especially neutrophil leukocytes, lymphocytes and histiocytes within the tumor. Neither necrosis nor vascular or perineural invasion was found. The tumor was located in the dermis without connection to the epidermis. The overlying epidermis was hyperplastic with reactive changes, acanthosis, and hyperkeratosis. The tumor was unencapsulated and focally grew in an infiltrative manner into the surrounding dermis. Focally, there were readily apparent smaller satellite tumor nodules.

Electronmicroscopically, prominent electron-dense cytoplasmic granules were abundant in the tumor cells and contained secondary lysosomes with heterogeneous lysosomal contents (Fig. 7). Nuclei were both centrally and eccentrically located, and there was margination of nuclear chromatin. Nuclei varied in shape from round to irregular and indented.

DISCUSSION

AFX is a rapid-growth solitary dermal tumor usually located in the dermis with a minimal extension to the subcutaneous fat, which is commonly regarded as a superficial variant of malignant fibrous histiocytoma. The tumor is most often associated with actinic damage. The histogenesis of the AFX is controversial. The results of electron microscopic and immunohistochemical studies indicate that the AFX as well as MFH arises from the progenitor, undifferentiated mesenchymal cell, capable of histiocytic, fibroblastic, and myofibroblastic differentiation (2).

Diagnosis of AFX should be regarded as a diagnosis of exclusion and achieving the correct diagnosis requires an immunohistochemical analysis using a panel of antibodies (10). The differential diagnosis is broad and includes a variety of malignant tumors such as spindle cell squamous cell carcinoma, leiomyosarcoma, pleomorphic liposarcoma, malignant peripheral nerve sheath tumors, extraosseous osteosarcoma, pleomorphic or spindle cell melanoma, spindle cell variants of angiosarcoma, and pleomorphic rhabdomyosarcoma (7).

AFX is positive only for some nonspecific markers, such as vimentin, CD68 and CD10. The focal expression of actin, EMA, and CD31 has been described (10). Moreover, the tumor cells are positive for some proteolytic enzymes, which include alpha-1-antitrypsin and alpha-1-antichymotrypsin, lysosome and cathepsin (4).

More specific immunohistochemical markers such as desmin, S-100, HMB45, Melan-A, and a panel of keratins must be used to exclude other pleomorphic tumors (5,6).

Despite the initial reports that CD99 and CD117 can be helpful in the differential diagnosis of AFX from MFH, further research fails to support their specificity and sensitivity (3,9,11). However, AFX is centered in the dermis and shows only a minimal extension into the superficial subcutis in contrast to superficial MFH which, by definition, is centered in the subcutaneous fat, although extension into the dermis is not uncommon (6). CD10 positivity may be helpful in the diagnosis of AFX, especially when there is strong, diffuse staining, but the specificity is low (9).

In our report, we described a case of AFX with granular cells. The only five cases of granular cell variant of AFX that have been described previously, have been mostly single-case reports (5,11,12). Based on the rarity of the reported cases, it would appear that these changes occur only on rare occasions. However, in a recent study of 66 cases of AFX, granular cell changes were found in 15 cases (22.7%), so it seems that this variant of AFX could be under-recognized (10). Unfortunately, the authors have not quantified these changes, so it is not clear if there were only focal granular cell changes, or it was rather a diffuse phenomenon. The granular cell variant of AFX consists of cytologically pleomorphic tumor cells with abundant eosinophilic granular cytoplasm. In several of the reported cases, the cytoplasmic granules were stained with periodic acid-Schiff (PAS) after diastase digestion. However, in other cases, including ours, the granules were PAS negative. Similar granular cell changes occur in a variety of other tumors such as basal cell carcinoma, leiomyoma, leiomyosarcoma, dermatofibroma, dermatofibrosarcoma protuberans, and angiosarcoma. However, granular cell changes may not only be the result of lysosomal accumulation, but can also be related to aging, metabolic alteration, increased apoptosis, cytoplasmic autophagocytosis, and more (13). In the granular cell variant of AFX, the granular cells are negative for S-100 in contrast to the granular cells of malignant granular cell tumors that are diffusely S-100 protein positive.

AFX is regarded as a tumor with a favorable prognosis, if strict criteria are followed. Tumors with atypical features (significant extension into adipose tissue, necrosis, and vascular invasion) are best regarded as potentially malignant (12). Although local recurrences do occur, only approximately 25 cases of metastasizing AFX have been reported to date (8).

In conclusion, we described another case of the granular cell variant of AFX. Despite its rarity, we should be aware of the possibility of granular cell change occurring in AFX to avoid misdiagnosis regarding other granular cell tumors.

ACKNOWLEDGMENTS

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OSOBNÍ SDĚLENÍ

Prof. MUDr. Josef Stejskal, CSc. 6. srpna 1926 - 3. prosince 2013



S pocitem smutku nad ztrátou pana profesora Stejskala mu vzdáváme poslední poctu. Profesor Stejskal, významná osobnost v historii české patologie, nás opustil počátkem prosince loňského roku po pozvolné ztrátě sil. Pan profesor si zvolil náš obor jako svoje životní poslání, upřednostnil jej před volbou stát se chirurgem a od studentských let obor neopustil. Cesta na univerzitní pracoviště vedené tehdy docentem B. Bednářem v Hlavově ústavu vedla z Plzně přes Oddělení patologie Thomayerovy nemocnice v Krči. Během svého působení v Hlavově ústavu a následně také ve Spojených státech v Chicagu se stal významným a uznávaným specialistou v nefropatologii. Ústav patologie 2. lékařské fakulty (tehdy Fakulty dětského lékařství) vedl od roku 1974 do roku 1992. Za dobu svého působení na našem pracovišti rozvinul histopatologickou a elektronmikroskopickou diagnostiku poruch ledvin u dětí a u dospělých, spolupracoval také velmi úzce s Klinikou dětské onkologie v oblasti patologie nádorů dětského věku. Svou trpělivou a skromnou, přitom důležitou práci si vysloužil úctu a respekt svých klinických spolupracovníků. Byl široce znám v obci patologů nejen v rámci české a slovenské společnosti, ale patologům z celé Evropy a ze zámoří prostřednictvím čilých mezinárodních styků, které v dobách předrevolučních nebyly vždy snadno udržitelné. Kromě této aktivity byl výborným učitelem s nezapomenutelným vtipným smyslem pro poutavé vyprávění příhod, kasuistik a životních zkušeností.

Pan profesor působil na našem pracovišti až do roku 2012, dvacet let po svém penzionování. Ještě v devadesátých letech učil paralelku mezinárodních studentů, přednášel patologii ledvin pro české i anglicky hovořící studenty a po mnoho let po svém odchodu do penze se také věnoval vyšetřování biopsií ledvin u dětských pacientů. Síly pana profesora postupně opouštěly a od roku 2012 zůstával v domácí péči.

Život pana profesora Stejskala byl bohatý a kromě pracovního vytížení se věnoval rybaření, zejména v oblasti svého letního sídla na Berounce a také fotografování. Fotografování bylo jeho celoživotním koníčkem nejen v soukromí pro radost, ale i v oblasti profesní fotografie mikroskopické.

Jeho žáci z našeho pracoviště i mimo ně mohli po mnoho let čerpat z jeho noblesního vystupování a jednání, a učit se od něj jako od svého vzoru významného učitele Karlovy Univerzity.

Čest a úcta památce pana profesora MUDr. Josefa Stejskala, CSc.

Za mateřské pracoviště
Roman Kodet