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ULTRASTRUCTURE OF ATYPICAL FIBROXANTHOMA

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Electron microscopic examination of an atypical fibroxanthoma (AFX) confirmed the fibrohistiocytic nature of this lesion. Ultrastructural evidence suggested a transition from fibroblasts to large giant cells with intermediate forms exhibiting features of both. A comparison of AFX ultrastructural features to those of other similar neoplasms suggested a possible relationship to malignant fibrous histiocytoma. As diagnosed by light microscopy, AFX probably represents a spectrum of neoplasms; this concept is discussed. It is urged, when possible, that electron microscopy be performed on lesions diagnosed as atypical fibroxanthoma since ultrastructure studies represent the most valid basis on which a correct diagnosis can be made.

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THE TERMINOLOGY OF ATYPICAL FIBROXANTHOMA (AFX) has been used by Helwig at the Armed Forces Institute of Pathology (AFIP) since at least 1956, and he subsequently described the disease in 1963 as a benign fibrohistiocytic process despite its malignant histology.⁶ Lund and Kraus were the first to make reference to AFX in the AFIP fascicle on Melanotic Tumors of the Skin.¹³ Subsequently, much has been written about this lesion, with confusion concerning its histogenesis.^{2,3,6,8,10,11,13,15,16,17} Nodular amelanotic malignant melanoma, several types of sarcoma, and metastatic carcinoma may be difficult to differentiate from some examples of AFX. Spindle cell squamous carci-

noma may be indistinguishable from AFX by light microscopy and differentiation requires use of the electron microscope.¹ A recent report of metastatic AFX indicates that ultrastructural studies are imperative to substantiate the light microscopic diagnosis.¹⁰ The purpose of this paper is to describe the ultrastructural features of an AFX, which, to the best of our knowledge, have not been previously reported. These observations confirm the fibrohistiocytic origin of AFX.

CASE REPORT

A 78-year-old Caucasian man was first seen in July, 1975, with a 1-month history of a rapidly growing lesion located on the left ear. Physical examination revealed an 8mm. purple, crusted nodule involving the left anthelix. A biopsy was obtained, followed by curettage and desiccation of the lesion. The biopsy sections were interpreted as atypical fibroxanthoma. The patient did well until January, 1976, when he first noted a nodule at the previously involved site. A repeat biopsy was interpreted as recurrent AFX. The lesion was excised and atypical cells were identified at the deep surgical cut margins. In August, 1976, the patient again noted a regrowth of the lesion, which was re-excised. One month after excision the surgical site appeared well healed.

MATERIALS AND METHODS

All specimens for light microscopy were fixed in 10% neutral buffered formalin and processed routinely; sections were cut for hematoxylin-eosin (H&E)-stained slides. A portion of the first recurrent lesion was initially fixed in 2.5% glutaraldehyde with 0.15 molar phosphate buffer, postfixed in 1% osmium tetroxide in Millonig

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FIG. 1. Low magnification showing dermal tumor nodule with overlying epidermis exhibiting collarette formation (H&E; $\times 20$).

buffer, dehydrated in graded ethanol, and embedded in Epon 812. Semithin ($0.5\ \mu\text{m}$) sections of the tumor were prepared and stained with toluidine blue. Ultrathin sections were cut on a Sorvall microtome, stained with uranyl acetate and lead citrate, and examined on an RCA electron microscope.

RESULTS

Gross Observations

Excision tissue taken from the first recurrence was oval-shaped, measuring $3 \times 2 \times 2\ \text{cm}$. Within the central portion there was a firm, smooth, round nodule approximately 1 cm in greatest dimension located 0.4 cm from one lateral surgical cut margin. On transection the nodule appeared homogeneously gray-tan. Two smaller masses, both approximately 0.5 cm in greatest dimension, were located adjacent to the nodule.

Light Microscopic Observations

Examination of sections prepared from the first recurrence were interpreted as showing the microscopic features of atypical fibroxanthoma. The lesion had a nodular configuration with an intact epidermis overlying a well-demarcated tumor mass (Fig. 1). The epidermis was atrophic with the exception of a small foci of collarette formation. The tumor mass abutted, but did not involve the epidermis. No downward streaming of squamous keratinocytes was identified in the sections available for study (Fig. 2). The tumor was composed of a pleomorphic population of cells. Many of the cells were large and appeared xanthoma-like with foamy, vacuolated, eosinophilic cytoplasm and vesicular basophilic nuclei. Some of the cells were multinucleated and ex-

hibited features similar to those of Touton-type giant cells. (Fig. 3). Approximately one mitotic figure per five high power fields was identified in the sections available for study. A second population included cells that were smaller, elongated, and spindle-shaped, and resembled plump reactive fibroblasts. These cells exhibited some variation in size, shape and staining characteristics and rarely contained mitotic figures. Some reactive histiocytes exhibited features of both xanthoma-like giant cells and small fibroblasts. Throughout the proliferative nodule there were strands of eosinophilic dense collagen and mild inflammatory infiltrate of lymphocytes and plasma cells (Fig. 2). A small amount of dermis adjacent to the cellular nodule exhibited vascular ectasia, capillary, endothelial proliferation, and solar elastosis.

Electron Microscopic Observations

At low magnification (Fig. 4), the tumor appeared to be composed of many xanthomalike giant cells filled with vacuoles which were incompletely surrounded by a trilaminar membrane. The vacuoles were generally round, but many were irregular and appeared fused with one another. The vacuoles were generally clear with scattered flocculant material, myelin figures, glycogen-like particles and dense bodies (Fig. 5). The same cells were surrounded by wide extracellular spaces containing bundles of dense collagen. No melanosomes, junctional complexes, or tonofilaments were identified in the sections studied. Many large histiocytes and xanthoma-like giant cells showed filopodia or delicate finger-like cytoplasmic projections on their surfaces (Fig. 6). These filopodia indicated that the cells were actively pinocytotic. Many

FIG. 2. There is no evidence of downward streaming of squamous keratinocytes. The tumor is composed of a pleomorphic population of xanthoma-like giant cells, large histiocytic cells, and spindle-shaped cells. Note strands of proliferating collagen and superimposed inflammatory infiltrate composed primarily of lymphocytes (H&E, $\times 120$).

vacuoles within these cells were probably present as a result of fusion of multiple pinocytotic vesicles. The surrounding cytoplasm was dense and contained scattered short profiles of non-dilated granular endoplasmic reticulum, small mitochondria with plate-like cristae, glycogen-like particles and many randomly oriented thin filaments (Fig. 5). At least two types of small cells were identified. The first type was similar to ordinary fibroblasts except they appeared morphologically more active. They were plump and contained many free polyribosomes or an extensive network of granular endoplasmic reticulum, which was dilated and filled with amorphous dense material (Fig. 7). The second type of small cell (Fig. 8) was spindle to oval-shaped, and contained many filopodia similar to those seen on the surface of larger histiocytes. Within the cytoplasm were dense bodies, thin filaments, vacuoles and also other organelles seen in larger giant cells (Fig. 9). This cell was considered to be a transitional one between fibroblasts and xanthoma-like giant cells. This interpretation was supported by the presence of vacuoles that

were similar to those seen in giant cells and suggested a progressive transition of small cells into giant cells. Both types of small spindle cells were associated with extracellular bundles of loose collagen and appeared to be involved actively in the production of ground substance matrix.

DISCUSSION

The clinical and light microscopic observations of AFX have been well documented.^{2,3,6,8,10,11,13,15,16,17} It is of interest that no previous electron microscopic studies have been reported. This, in part, may result from AFX not being clinically distinctive and because the diagnosis is usually made from formalin-fixed tissue embedded in paraffin. In our case the lesion recurred and this allowed the opportunity to process tissue initially for electron microscopy. The ultrastructural features fit those of a fibrohistiocytic reaction, and are not those of epithelial neoplasms, malignant melanoma, or other tumors usually considered in the differential diagnosis

FIG. 3. High power magnification of tumor cells illustrating multiple spindle-shaped cells, some resembling fibroblasts and others resembling xanthomas cells (H&E, $\times 250$).

FIG. 4. Large xanthoma cell. These cells are surrounded by dense collagen (c) and contain many vacuoles which are generally round and clear ($\times 3,800$).

FIG. 5. Cytoplasm of intermediate-sized cell. The cytoplasm contains forming pinocytotic vesicles (p), irregular vacuoles (v) and others with myelin figures (m) and flocculent material (f) ($\times 24,900$).

of AFX. The presence of xanthoma-like giant cells and intermediate forms clearly suggest a transition from the smaller fibroblastic cells providing a unifying histogenesis for AFX. Of the two types of small cells seen, one has ultrastruc-

tural characteristics of hyperactive fibroblasts. The other type of small cell suggests a transitional cell with combined features of fibroblasts and histiocytes.

The ultrastructural features of AFX appear

FIG. 6. Intermediate-sized histiocyte. The cell appears actively pinocytotic and has many filopodia (f) on its surface and intracellular vacuoles ($\times 7,800$).

FIG. 7. Small fibroblasts. The cell on the left is plump and contains many polyribosomes and the one on the right is filled with dilated cisternae of granular endoplasmic reticulum ($\times 8,400$).

similar to those features described for possibly related lesions. Electron microscopic studies of xanthomas reveal fibroblasts, xanthoma cell, and combinations of both.^{9,19} Xanthomas do not exhibit the active small cells. A lesion considered

by some observers to be related to AFX is pseudosarcoma of the skin.² The major distinctive electron microscopic feature of pseudosarcoma is a cell population of fibroblasts or myofibroblasts with no significant histiocytic or

FIG. 8. Transitional cell form. The surface has filopodia (f) and the cell is associated with newly formed matrix (m) ($\times 10,000$).

FIG. 9. Higher power of a transitional cell form. The cytoplasm contains vacuoles (v) scattered short profiles of granular endoplasmic reticulum (er), mitochondria (m) and Golgi apparatus (g). The nucleus (N) is irregular and contains blocks of dense heterochromatin ($\times 27,800$).

xanthomatous component.¹⁸ Others have interpreted ultrastructural morphologic criteria of pseudosarcoma to be consistent with a tumor of epithelial origin, particularly a spindle-cell variant of squamous carcinoma.¹² Our observations of AFX did not reveal abortive keratohyalines, desmosomes, or tonofilaments. Of the tumors examined by electron microscopy, malignant fibrous histiocytoma appears most similar to AFX.⁴ In our case of AFX, nuclear bodies, maculae adhaerentes, and primitive stem cells were not present although other ultrastructural features appear similar. Most of the surface characteristics, cytoplasmic organelles, and the presence of intermediate or transitional forms are identical in malignant fibrous histiocytoma and AFX.

We believe that AFX, as diagnosed by light microscopy, represents a heterogeneous population of neoplasms. One portion consists of sarcomas, malignant melanoma, metastatic carcinoma, and spindle cell squamous cell carcinoma. The number of these misdiagnosed cases should be small if interpretations are made by an experienced pathologist who correlates the clinical features with light microscopic and histochemical characteristics. Another portion consists of pseudosarcomas. Many authors feel strongly that pseudosarcomas are either purely

epithelial or mesenchymal in origin.^{2,5,7,12,14,18} On the basis of their observations, we believe that most pseudosarcomas are lesions in which malignant epithelial cells, such as from a spindle cell squamous carcinoma, are intermingled with a reactive, cytologically atypical stromal component. This interpretation would tend to explain some of the divergent diagnoses reached when examining some lesions considered to be an AFX. The third and probably the largest sub-group of neoplasms in this heterogeneous group are true atypical fibroxanthomas. These are pure fibrohistiocytic lesions as supported by our ultrastructural observations. These lesions resemble malignant fibrous histiocytomas ultrastructurally as well as by conventional light microscopy. Although the biological behavior of these tumors is different, this could be related to dermal tumor location for AFX and generally deeper tissue involvement of malignant fibrous histiocytoma.

It is hoped that more lesions diagnosed as AFX, and particularly metastatic AFX, will be studied by electron microscopy. It appears that by light microscopy AFX represents a heterogeneous group of neoplasms. True AFX is a fibrohistiocytic lesion and currently the most valid basis for confirming this diagnosis is by electron microscopy.

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