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SOLITARY ADULT XANTHOGRANULOMA: A CASE REPORT WITH NEW OBSERVATION ON LIPID DROPLET FORMATION

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Abstract. A case of solitary xanthogranuloma was studied by optical and electron microscopy. The tumor parenchyma cells were composed mainly of multilocular lipid droplets together with rough-surfaced endoplasmic reticulum, a few mitochondria, glycogen particles, and fine filaments sparsely scattered throughout the cytoplasm. The parenchyma cells bore a close structural resemblance to Ito's "fat-storing cells" which are situated in Disse's space, contain lipid droplets and are thought to be the only cells participating in intralobular fibrillogenesis in the liver. Another notable finding was that the lipid droplets of the tumor parenchyma cells originated directly from rough-surfaced endoplasmic reticulum. Thus, the tumor morphology was incompatible with the currently favored concept of a benign, reactive non-neoplastic process of prominently histiocytic cells, being characterized instead by prominently fibroblastic cells.

Key words: Solitary adult xanthogranuloma; Xanthogranuloma; Lipid droplet; Lipogenesis; Fat-storing cell

Solitary adult xanthogranuloma (SAX) was first described in the literature by Rodriguez et al. in 1976 (12). "Juvenile xanthogranuloma" was said to have essentially the same histology irrespective of whether found in children or adults, and whether of multiple type or solitary type (12). However, the pathogenesis of SAX and other tumors of this kind has not been elucidated. The present observations focus on the ultrastructure of the tumor parenchyma cells, and the discussion considers the origin of the tumor together with the morphogenesis of the lipid droplets.

MATERIALS AND METHODS

A 31-year-old Japanese male with a solitary lesion in the left lateral abdominal region observed a rapid increase in size of the lesion over a period of 3 months. The lesion was a protruding semispherical papule, measuring 9×9×9 mm, and appeared to be a slightly yellowish brown elastic tumor crowned with thin, circinate, whitish scales (Fig. 1). The clinical diagnosis was possibly xanthoma tuberosum or histiocytoma. The lesion was excised whole and histologically diagnosed as xanthogranuloma. It was finally diagnosed as SAX (12) by a combination of the histological and clinical findings. Physical examination of the patient failed to reveal evidence of concomitant involvement, and the serum lipid and other laboratory data were found to be normal.

Light microscopy

Paraffin-embedded tissue was stained with hematoxylin-eosin stain, van Gieson's stain, Weigert's elastic fiber stain, Prussian blue stain, and PAS stain with and without diastase digestion. Sudan III staining was carried out with formalin-fixed cryostat sections.

Electron microscopy

The tissue was cut into 1 mm^3 cubes, fixed in 2% glutaraldehyde in 0.1 M phosphate buffer (pH 7.4) for 3 hours, and soaked in 2% sucrose 0.1 M phosphate buffer (pH 7.4) overnight. The cubes were then post-fixed with 1% osmic acid in the same buffer for 2 hours, dehydrated in graded ethanol, and embedded in Epon 812 *ad modum* Luft (7). Sections were cut in an LKB ultramicrotome and double-stained with uranyl acetate and Reynold's lead citrate. The stained sections were observed in a JEM-100B electron microscopy with an accelerating votage of 80 kV.

RESULTS

Light microscopy

The tumor mostly protruded above skin level. A localized, richly cellular, unencapsulated growth diffusely invaded the dermis; in addition to the pro-

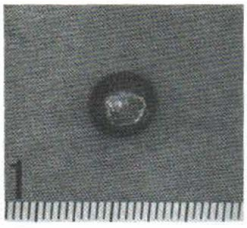


Fig. 1. Photograph of lesion.

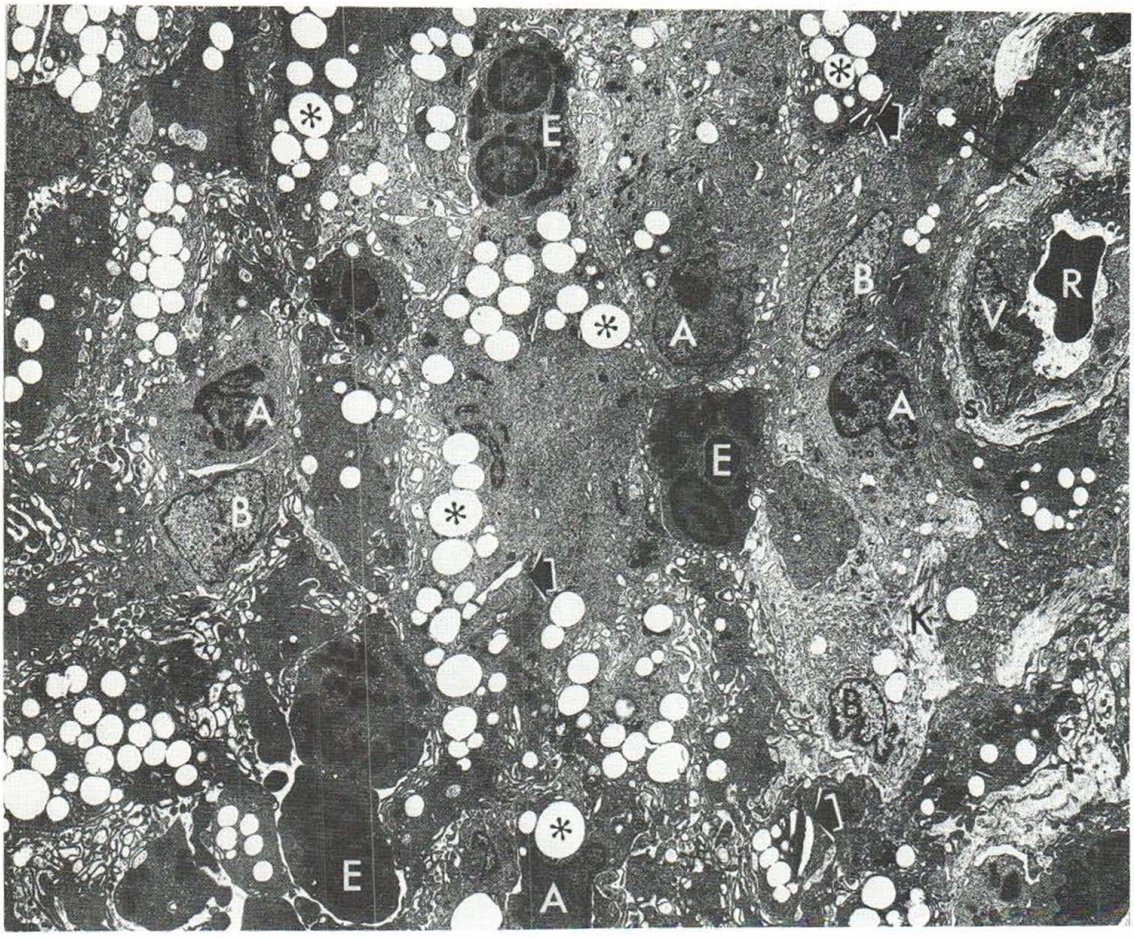


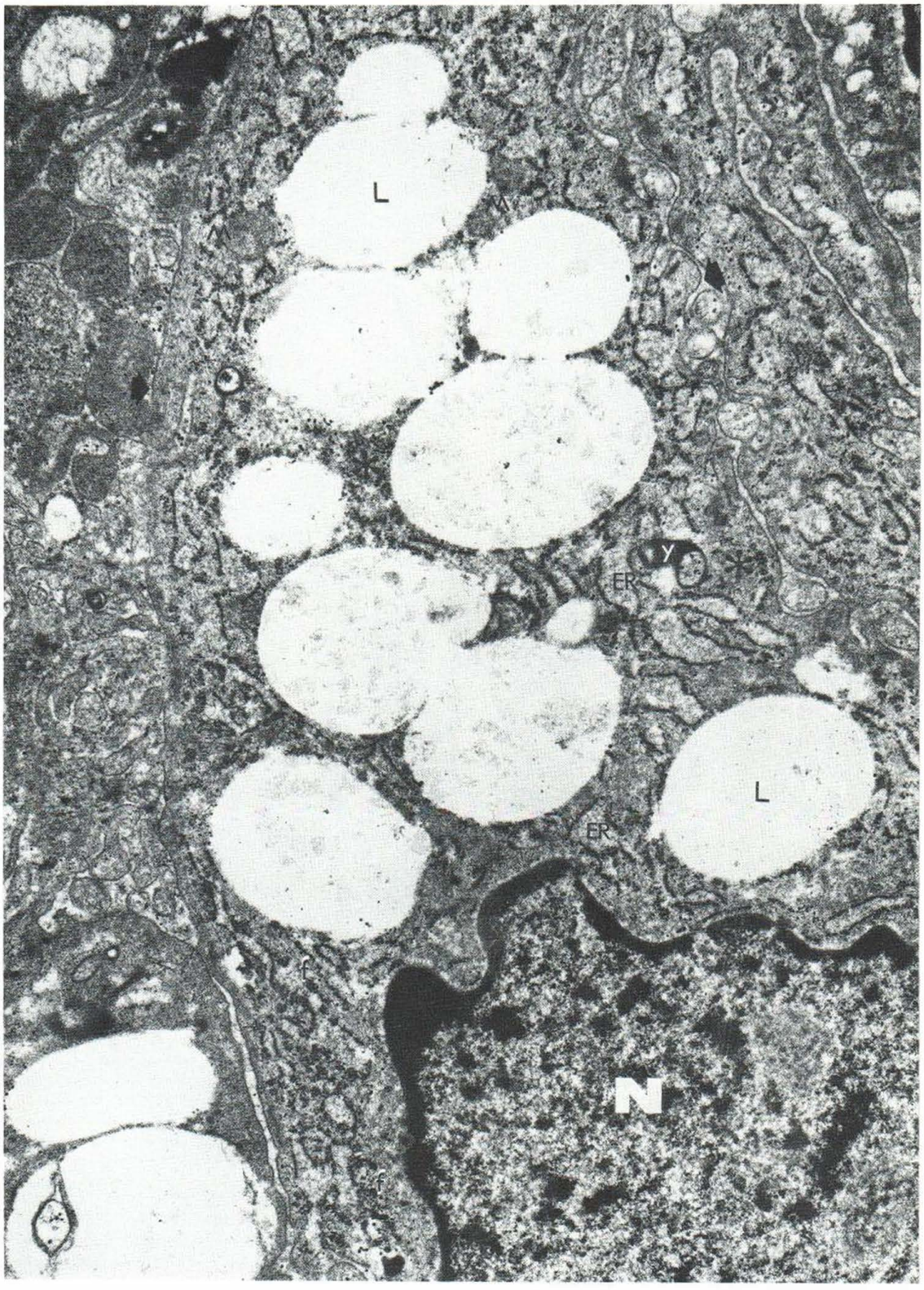
Fig. 2. Low magnification micrograph. The parenchyma consists of multilocular lipid vacuoles (asterisk) containing cells (*A*, *B*) except for the infiltration of eosinophils (*E*) sparsely scattered throughout the tumor. Thick arrow, cholesterol cleft; *V*, capillary wall; *R*, erythrocyte; Double arrow, multilamination of capillary basal laminae; *s*, pericapillary area. ×3 300.

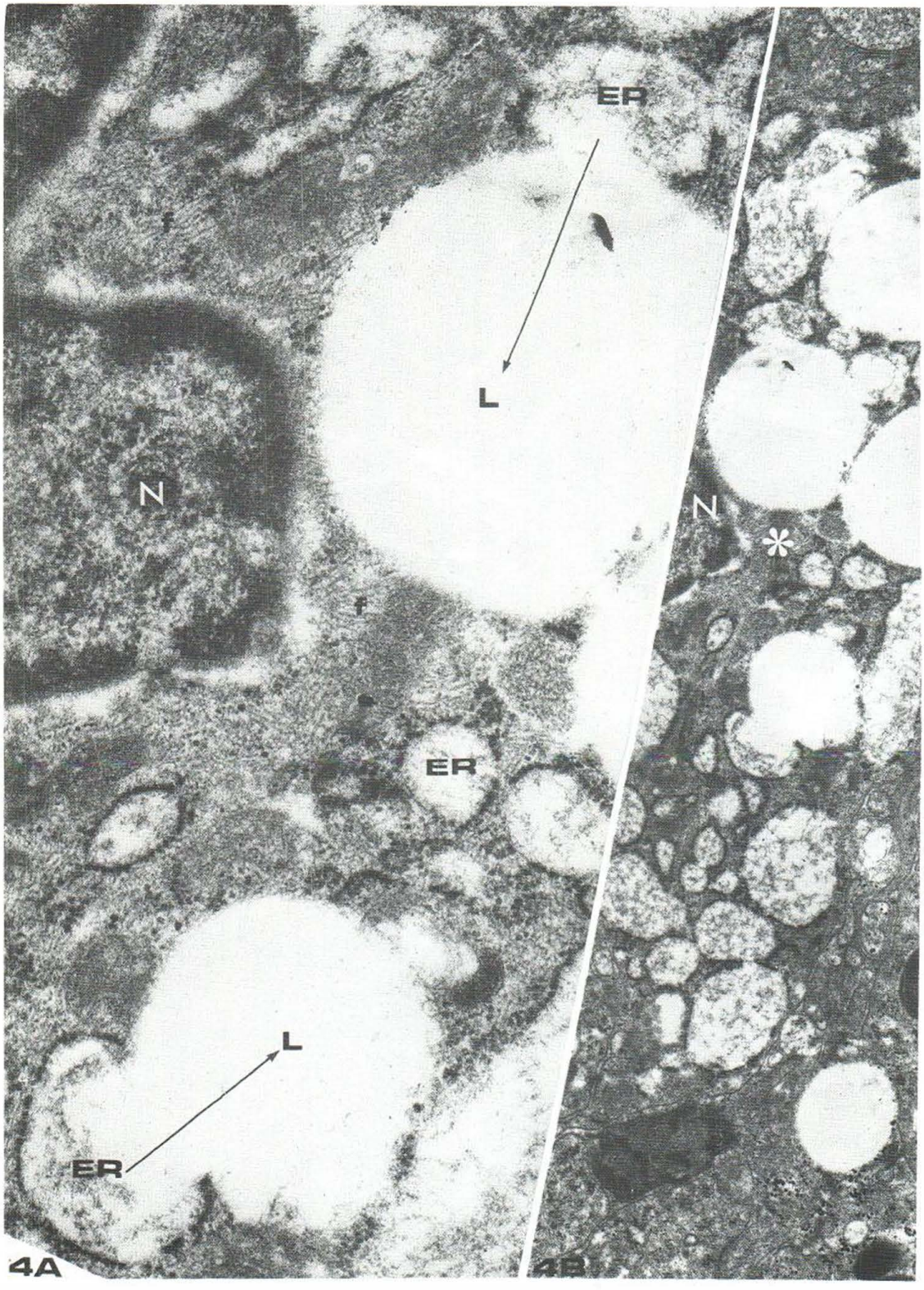
liferating histiocytic and foamy cells, the parenchyma contained lymphocytic cells, fibroblastic cells, and many scattered eosinophils. Although the histiocytic cells contained active nuclei, no true atypical features or signs of polymorphism were found. Lymphocytes and plasma cells were scarce. Touton-type giant cells were found, though only in small numbers. No PAS-positive substances were found in the foamy cells, many of which stained with Sudan III stain in the same way as fully differentiated cells. A small amount of collagen fiber was found with van Gieson's stain, but no elastic fibers were detected by Weigert's elastic fiber staining of the stroma. Prussian blue staining (for iron) was negative. The tumor was thus clearly distinguished from dermatofibroma, histiocytoma, reticulohistiocytoma (reticulohistiocytic granuloma), Hand-Schüller-Christian disease, and tuberous xanthoma (6).

Electron microscopy

The tumor consisted mainly of lipid vacuole-containing parenchyma cells (LVC), together with infil-

Fig. 3. A representative parenchyma cell containing ten lipid vacuoles (*L*) and well developed; also shown is the more or less dilated rough-surfaced endoplasmic reticulum (*ER*), among which diffusely scattered fine filaments (*f*), glycogen particles (asterisk), mitochondria (*M*), and one lysosome (*y*) are observed. *N*, nucleus; Thick arrow, micro-villus. ×52 000.


L
Y
ER
L
ER
N


ER
L
N
f
f
ER
L
ER
N
*
4A
4B

trated eosinophils diffusely scattered throughout the tumor ("E" in Fig. 2). The LVC comprised two polar types of cell ("A" and "B" in Fig. 2), one ("A" in Fig. 2) being mature and the other ("B" in Fig. 2) less mature. Both contained multilocular lipid vacuoles and had the same kind of cell organelles, though their number differed according to the degree of maturation of the LVC. The cell organelles other than lipid vacuoles were rough-surfaced endoplasmic reticulum (rER), mitochondria, Golgi complex, centrioles, lysosomes, glycogen particles, and fine filaments. The cholesterol clefts found in the cytoplasm embedded in each matrix varied in size from 400 to 1 200 nm (thick arrow in Fig. 2). The matrices of the cholesterol clefts were free from lipid vacuoles and lysosomes. Interstitial fibrous tissues were scarce ("K" in Fig. 2). Capillaries ("C" in Fig. 2) were occasionally found. The endothelial cells appeared normal, showing no evidence of vacuolization despite abundant lipid vacuoles in the stromal cell—LVC—around the vessel. The pericapillary spaces ("s" in Fig. 2) appeared loosely textured due to lucent areas suggesting edema, and showed replication of stratified basal lamina, suggesting rapid regeneration (9, 10) of the endothelial cells (double arrow in Fig. 2). In those areas where the LVC were closely packed, the projections of adjacent cells intertwined, some of the LVC borders being attached by desmosome-like structures. The latter were about 90 nm long and the opposed plasma membranes were separated by a parallel distance of some 40-60 nm. Intercellular contact layer-like structures from 10–15 nm thick were occasionally found in the middle of the opposed plasma membrane.

An LVC containing a fair number of lipid vacuoles is shown in Fig. 3. Well-developed rER ("E" in Fig. 3) and lipid vacuoles were observed throughout the cytoplasm, together with a small number of mitochondria ("M" in Fig. 3), lysosomes ("y" in Fig. 3), glycogen particles (Asterisk in Fig. 3), and fine filaments ("f" in Fig. 3). Most of the rER were more or less dilated. A parallel array of elongated flattened rER showing a lamellar pattern was occasionally observed (Fig. 3). No surrounding basal lamina was found, and the plasma membrane occasionally formed microvilli or thin projections (Thick arrow in Fig. 3); pinocytosis and vesiculation of the peripheral cytoplasm were rare.

It is clear from the foregoing findings that the LVC exhibit no sign of phagocytic activity. Further, neither the rod-like tubular structures 6–7 nm in diameter nor disc- or plate-like structures 40–50 nm in thickness characteristic of histiocytosis X could be detected. Were the lipid vacuoles found in this study absent, the LVC would resemble a fibroblast rather than a histiocyte. Thus, in this respect, the tumor parenchyma cell (LVC) was very similar to Ito's "fat-storing cell" (4), which is thought to play a leading part in intralobular fibrillogenesis of the liver and is thought to be one of the so-called fibroblast-like cells, such as lung interalveolar cells, and kidney interstitial cells (5). Fig. 4 A (an enlargement of the asterisk area in Fig. 4B) could be interpreted as showing that vacuoles come from dilated rER.

Thus, the area marked by an arrow in Fig. 4 A was thought to represent the formation of the initial stage of a lipid vacuole ("L" in Fig. 4 A) derived exclusively from rER ("ER" in Fig. 4 A). In addition to rER and lipid vacuoles, fine filaments some 90 to 120 nm in diameter were scattered throughout the cytoplasm (Fig. 4 A). Fig. 4 B has been presented to show more clearly the origin of the lipid vacuoles and the relationship with rER in Fig. 4 A. The rER showed some variation of density, which revealed a tendency to diminish in dilated rER, that is in lipid vacuoles (Fig. 4 B). This would also support the view that parenchyma cells derive from one of the so-called fibroblast-like cells.

DISCUSSION

The literature on solitary adult xanthogranuloma (SAX) is relatively scant (12). No electron microscopic studies of SAX have been documented. Light microscopy of SAX was said to reveal the same findings as other kinds of xanthogranuloma, multiple as well as solitary, irrespective of whether found in children or adults (12). According to the electron microscopic study of juvenile xantho-

Fig. 4 A. Enlargement of the asterisk area in Fig. 4 B, showing that lipid vacuoles (*L*) originate directly from dilated rough-surfaced endoplasmic reticulum (*ER*). *N*, nucleus; *f*, fine filament. ×46 000.

Fig. 4 B. Presented to assist understanding of Fig. 4 A. *N*, nucleus. ×15 000.

granuloma by Gonzalez-Crussi & Campbell (2) in two cases diagnosed in a 9-month-old male child and a 3-year-old girl, the parenchyma cells consisted exclusively of histiocytic cells and the ultrastructure appeared to differ from both eruptive xanthoma and lesions of histiocytosis X (2). Furthermore, the origin of the lipid accumulation could not be identified (2).

In the present study, however, the parenchyma was composed exclusively of fibroblastic cells and it was demonstrated that the lipid vacuoles originated from rER by *de novo* synthesis in the parenchyma cells. The possibility that the parenchyma cells derive from the pericyte is discounted by the fact that a basal lamina could not be detected around the parenchyma cells. The parenchyma cells showed no sign of phagocytosis, and the organelles most characteristic of histiocytic cells, such as smooth-surfaced endoplasmic reticulum and Birbeck granules, were entirely undetectable.

The cell organelles characteristic of the parenchyma cells in the present study were rER, fine filaments, and multilocular lipid vacuoles.

Thus, the parenchyma cells were very similar to the "fat-storing cell" first documented by Ito et al. in 1952 (3). The fat-storing cell (FSC) is invariably situated in Disse's space and has a relatively well-developed Golgi complex containing a diplosome, sparse small mitochondria, fairly well-developed elements of rER, small lysosomes, glycogen particles and occasionally a single cilium (4). Moreover, the FSC contain multilocular lipid droplets as constant and characteristic cytoplasmic inclusion bodies (about 2 μm in diameter), none of which fuse together into larger ones (4). Possible functions of the FSC proposed by Ito et al., are (4): 1) Lipid synthesis and lipid droplet formation, 2) Storage of lipid droplets and fat-soluble vitamin A (8, 11), 3) Participation in intralobular fibrillogenesis and 4) Reinforcement of the endothelial lining of the sinusoid with a subendothelial process.

The FSC is the one of the fibroblast-like cell group which contains, in addition to FSC, lung septal cells and kidney interstitial cell (5). These are said to be mesenchymal cells and constantly exhibit *de novo* synthesis of intracytoplasmic lipid droplets as well as a fibrillogenetic capability (5).

Because all the specimens had been fixed and embedded in paraffin or Epon 812, localization of vitamin A in the lipid droplets could not be determined in the present study (8, 11). However, the parenchyma cells of the tumor were consistent with fibroblast-like cells rather than histiocytic cells.

The new cytological findings of the present study have not previously been reported from xanthogranuloma of any kind, let alone SAX. Another interesting finding was that lipid droplets arise directly from rER by a *de novo* process.

The capillaries located in the tumor parenchyma showed no clear pathological signs such as degeneration, vacuolization or lipid surcharge. Multilamination of the capillary basal lamina can be interpreted as evidence of repeated stimuli (10) or regeneration (9) of the capillary walls. The multilocular lipid droplet material produced in the parenchyma cells was thought to reach the capillaries from the blood plasma of the patients, who had normal values—normolipaemia—in the laboratory examination. Although the β-sitosterol (1) level of the blood plasma and lesion could not be examined in this case, the possibilities of a tuberous and/or tendon xanthoma were clearly ruled out by both histological and ultrastructural evidence.

The present findings raise the possibility of SAX histopathogenesis as a tumor of fibroblastic cell origin, thus making SAX essentially different from other kinds of xanthogranuloma.

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