LIPOBLASTOMATOSIS: A TUMOR OF FETAL FAT DIFFERENT FROM HIBERNOMA

Report of a Case, with Observations on the Embryogenesis of Human Adipose Tissue *

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Tumors of adipose tissue are varied, and no classification of them is generally accepted. The tumors include true neoplasms, the lipomas and liposarcomas, and non-neoplastic masses.[1] Benign neoplasms of fat, lipomas are usually composed of mature fat cells; each cell is distended with a large vacuole of lipid which displaces the nucleus and compresses it against the cytoplasmic membrane. The so-called hibernoma is a tumor of adipose tissue, the component elements of which are multivacuolated and contain varying amounts of eosinophilic cytoplasm. These tumors resemble the brown fat of hibernating animals; hence their name. Cox[2] has suggested that tumors of brown fat are composed of immature adipose tissue.

It is now generally agreed that the lipoblast is a specialized cell differing from the fibroblast.[3] According to Shaw,[4] this theory was proposed by Todd and Bowman, in 1845, and supported by Toldt, in 1870. Subsequently others have held that adipose tissue is derived from the fibroblast, which elaborates fat. It has been suggested that fat in different sites is not necessarily similar, the notable exception being the brown fat found especially in hibernating animals.[5-9] According to Rasmussen,[7] brown fat in animals forms a large mass in the superior mediastinum. It extends into the intermuscular septums in the cervical region, with large lobes in the lateral portions of the neck. A pair of dorsal lobes is situated between the scapulas, and there are also extensions into the abdominal cavity with prominent perirenal lobes. In the human, the white fat encountered in the fetal and infantile periods resembles brown fat histologically.

Recently, we observed an unusual tumor, resembling fetal adipose tissue, in an 8-month-old child. This tumor was located in the subcutaneous tissue of the anterior wall of the thorax, the right axilla, and the right suprascapular area. It differed from hibernoma clinically,

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grossly, and microscopically, but was also distinctly different from tumors of adult adipose tissue. Histologically, the lesion resembled fetal fat, and the term "lipoblastomatosis" is proposed for this reason. A study of the development of adipose tissue in human fetuses was undertaken in order to gain a better understanding of the nature of this lesion.

Case History

An 8-month-old white girl was admitted to the Pediatrics Service of the James Whitcomb Riley Hospital, Indiana University Medical Center, on July 26, 1955. Five weeks before admission, her parents noted enlargement of the right arm and forearm. Before that, she was in good health, ate well, and grew satisfactorily.

Physical Examination. The right upper extremity was somewhat larger than the left, but was not increased in length. There was a faint pink discoloration; no cyanosis was noted. A soft swelling occupied the pectoral region and the axilla on the right side. The swelling appeared to increase with crying. No definite mass could be palpated. There was no limitation of motion of the arm and no pain. The axillary and brachial pulses were equal on both sides. The femoral and aortic pulses were good. Examination of the chest and abdomen showed no other abnormalities.

Laboratory Studies. The hemogram and urinalysis were normal. A postero-anterior roentgenogram of the chest revealed deformity of the right first rib, which was fused with the second rib anteriorly at about the junction of the rib and the costal cartilage. The possibility of venous or lymphatic stasis secondary to the rib abnormality was considered. A venogram revealed no obstruction of the circulation.

Clinical Course. Operative exploration of the affected region demonstrated a diffuse tumor in the subcutaneous tissue of the anterior part of the thorax, the areolar tissue of the right axilla, and the right supraclavicular area. As much of this tissue as possible was removed. Another mass, which was fairly well encapsulated, was found surrounding the brachial artery and vein and the cords of the brachial plexus. This was dissected free without injuring the adjacent structures. The postoperative course was uneventful. There had been no recurrence of the lesion on February 7, 1958.

Pathologic Examination

The specimen (I.U. # 77452) consisted of two masses measuring 4.5 by 3 by 1.5 cm. and 7 by 5 by 3 cm. The tissue was composed of numerous small, soft, pale gray lobules, most of which were several millimeters in diameter; some were as large as 1 cm. Portions of the lesions were myxomatous. The cut surface was greasy.

Histologically, a lobular pattern was evident, the lobules being joined by loose connective tissue. The lesion was richly vascular, and each lobule had its major vessel which arborized in a plexiform manner (Fig. 1). Many of the cells were vacuolated, and in some of these there was a large single vacuole displacing the nucleus against the cytoplasmic membrane. Smaller cells were multivacuolated and contained more centrally placed, round nuclei (Fig. 2). In such cells a moderate amount of granular eosinophilic cytoplasm intervened be-

tween the vacuoles. The vacuoles proved to be sudanophilic in frozen sections of formalin-fixed tissue.

In some sites, spindle-shaped and stellate cells lay in an abundant pale-staining stroma. These appeared more frequently at the periphery of the lobules (Fig. 1), and in some marginal lobules the entire content was of this nature.

Although the histologic appearance of the lesion resembled myxoid liposarcoma, its lobular arrangement, circumscription, and the absence of invasion into surrounding tissues served to distinguish it from this neoplasm. The lobulated pattern of the tumor simulated that seen in hibernoma, but differed in that there were numerous spindle-shaped and few polyhedral cells with granular, eosinophilic cytoplasm.

Embryology of Adipose Tissue

Material

Thirteen human fetuses in good state of preservation were studied. Eleven were specimens procured from spontaneous abortions, one was the product of a premature stillbirth delivery, and one was a full-term, stillborn infant. Four fetuses were 10 cm. or less in crown-to-heel length; one was 13.5 cm., two were 20 cm., two were 23 cm., and one each was 27 cm., 28 cm., 41 cm., and 48 cm. Specimens were fixed in neutral formalin. Sections of tissues from various sites were examined, especially samples from the axillary, interscapular, and mediastinal regions, the perirenal area, the buccal fat pad, and subcutaneous tissues in various sites. Paraffin sections were prepared with hematoxylin and eosin, Mayer's mucicarmine, and Alcian blue-periodic acid-Schiff stains. Frozen sections of some specimens were stained with Sudan IV.

Observations

No significant differences were evident in the mode of formation of adipose tissue in the various sites. However, fat appeared earlier in some locations than in others. The sites of earliest appearance were the subcutaneous region, the buccal fat pad, and the axilla. Adipose tissue in the mediastinum and retroperitoneal regions made its appearance and matured later.

The first change detectable histologically was the appearance of capillaries in relatively acellular primitive mesenchyme (Fig. 3). This was seen earliest in the subcutaneous tissues of some, but not all, fetuses of about 9 cm. crown-to-heel length. Plump, spindle-shaped and stellate cells were found adjacent to the capillaries. These cells had large nuclei and well defined, somewhat basophilic cytoplasm.

Vacuoles were difficult to identify in hematoxylin and eosin preparations, but with Sudan IV stain, minute, sudanophilic cytoplasmic vacuoles were noted. In these regions in older fetuses, very vascular lobules were present (Figs. 4 to 6), each surrounded by compressed mesenchyme. The entire mass of lobules comprising the buccal fat pad was invested by a dense capsule (Fig. 6).

In fetuses 20 cm. in length, the adipose tissue was well defined. The vascularized lobules were relatively cellular. Some of the cells were spindle shaped; others had multiple small vacuoles; still others contained a few larger vacuoles, and many contained one large vacuole with the nucleus displaced to one side. The latter were the most abundant elements present. Multivacuolated cells were uncommon.

In the fetuses 23 to 28 cm. in length, fat tissue was well established. Lobules appeared in the gross as small flecks of yellow in myxomatous stroma. This was the case in the buccal, mediastinal, axillary, and retroperitoneal regions where the yellow aggregates were limited by delicate membranes. Isolated lobules of fat were found developing in the mesenchyme between muscle bundles, but these were not visible grossly. Histologically, the adipose tissue at this age was clearly lobulated, and the lobules now abutted on one another. The cells were mostly univacuolated, signet-ring forms. At the periphery of the lobules, the cells were occasionally moruloid or lacked detectable vacuoles in hematoxylin and eosin stained preparations. This arrangement suggested that the cells at the periphery of lobules and at some distance from the larger vascular branches were younger in point of development. The adipose tissue at this age was still recognizably richly vascular and possessed an organoid pattern.

In later stages of development, fat was recognizable grossly as gray or yellow lobulated tissue. In various areas it extended by insinuating itself into crevices between other supporting structures (muscle), in this respect resembling the growth of capillary hemangiomas of infancy. Eventually the various collections of adipose tissue joined to form continuous masses.

The microscopic appearance of the fat in the 41 cm. and 48 cm. fetuses varied in appearance in different areas, but the lobular pattern was manifest. In the buccal fat pad and in most of the subcutaneous tissue, it was composed of fully developed fat cells, each with only one large vacuole. Much of the adipose tissue in the axillary, mediastinal and retroperitoneal regions, however, was composed of fat cells with multiple vacuoles and abundant intervacuolar eosinophilic granular cytoplasm (Figs. 9 and 10). The nuclei were centrally placed. These cells resembled the brown fat of lower animals.

Discussion

A survey of fetal tissues indicates that fat is a specialized substance derived from lipoblasts which, in turn, arise from perivascular mesenchyme. Wasserman[10] considered the lipoblast to be closely allied to the reticuloendothelial system and especially to the hematopoietic organ. Stout[11] cautioned that it was safer to regard the lipoblast as a fat-forming mesenchymal cell which could on occasion produce a wide variety of different and complex tissues.

Our observations indicate that adipose tissue in the human fetus develops in similar fashion in various locations, but that in the axillary, mediastinal, and retroperitoneal areas it does not attain adult form at the time of birth. The manner of maturation in the various sites is in accord with the description of the development of the buccal fat pad recorded by Scammon.[12] This author pointed out that early growth consisted of the expansion of enclosed mesenchymal and pre-adipose tissues; later growth was principally by increase in fat content. The latter included increase in number of fat lobules, formation of new fat cells, and growth of individual fat cells. According to Scammon, the formation of lobules in the buccal fat pad ceased by the fifth fetal month, at which time there were between 250 and 350 lobules. He felt that formation of new fat cells in this region ceased in later fetal life, usually by the seventh fetal month.

Whether lobules continue to develop in other sites in the late fetal and postnatal periods is not clarified by our study. It seems reasonable to suppose that a halt in the development of new lobules occurs in this period but that lipoblasts continue to be formed. The lesion in our case appears to have resulted from continued proliferation not only of lipoblasts but also of new lobules of adipose tissue in the postnatal period.

The case reported by Van Meurs[13] as an embryonic lipoma is similar to ours. Van Meur's patient was a 5-month-old child who had 4 recurrences of the lesion during 20 months following repeated excisions. All 5 of the specimens were similar, but with later operations, the tumor assumed the appearance of mature adipose tissue, a feature which the author considered a transformation of an embryonic lipoma to a common lipoma.

The case reported by Cox[2] as a hibernoma may be another example of this type of lesion. This was a 6-week-old male infant who died from asphyxiation due to the tumor in the neck. The author noted the similarity of the lesion to immature fat and considered it to be a hibernoma because of the presence of cells with eosinophilic granular cytoplasm. The illustrations in this report are difficult to evaluate. It

is notable, however, that other recorded instances of hibernoma occurred in adults.[2,8,14-18]

We suggest that the hibernoma is a tumor of fat cells in which the enzyme systems are incompletely developed. This differs from lipoblastomatosis, essentially a tumor of embryonic adipose tissue.

SUMMARY

An unusual tumor of embryonal fat tissue, designated lipoblastomatosis, is reported. This lesion appeared as a soft mass in the subcutaneous tissues of the anterior wall of the thorax and the areolar tissue of the axilla and supraclavicular regions of an 8-month-old girl. It was not encapsulated but infiltrated the area diffusely. It was composed of distinct lobules of embryonal adipose tissue; the fat content of the component cells varied. The tumor had not recurred after 30 months and was presumed to be benign.

A study of the embryogenesis of adipose tissue in human fetuses was undertaken in the light of this unusual neoplasm. Adipose tissue was first recognizable at certain locations in embryos at about 9 cm. in crown-to-heel length. Formation of fat lobules apparently ceases in the late fetal or early postnatal period, although formation of individual lipoblasts may continue. Fat cells in the axillary, mediastinal, and retroperitoneal regions may not attain adult form at the time of birth. Lipoblastomatosis apparently results from continued proliferation of lipoblasts and of new lobules of adipose tissue in the postnatal period.

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[*Illustrations follow*]

LEGENDS FOR FIGURES

All sections shown in the figures were stained with hematoxylin and eosin.

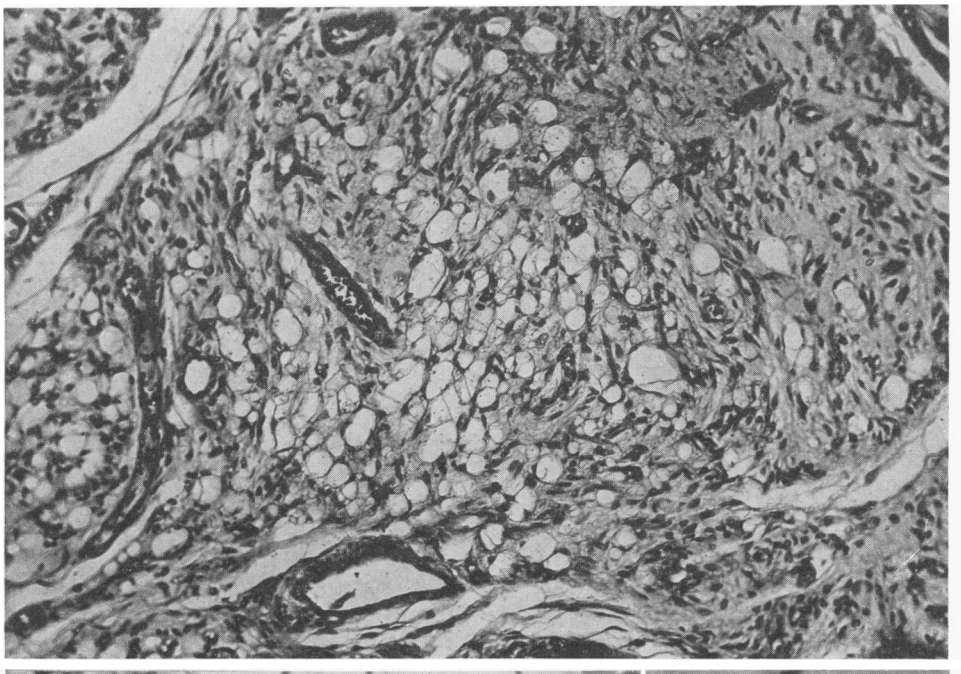
FIG. 1. Cells at the periphery of the tumor are immature, and those near the vascular pedicle contain large solitary vacuoles. × 100.

FIG. 2. A portion of the tumor in which almost all of the cells contain fat vacuoles of varied size. Some are multivacuolated. × 600.

FIG. 3. The earliest recognizable lobule of adipose tissue, in the subcutaneous tissue of an 8.5 cm. fetus. Some of the cells contain fat, demonstrable with Sudan IV, but not visible here. × 300.

FIG. 4. Adipose tissue in the subcutaneous tissue of a 20 cm. fetus. Some of the cells are vacuolated. × 150.

FIG. 5. Adipose tissue in the perinephric region of a 20 cm. fetus. × 150.



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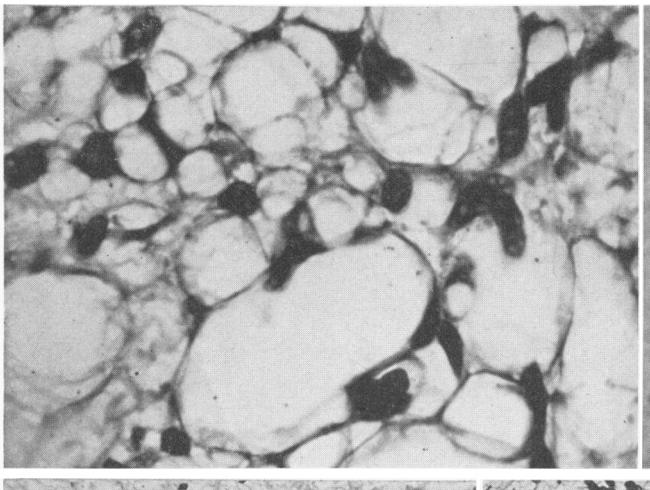

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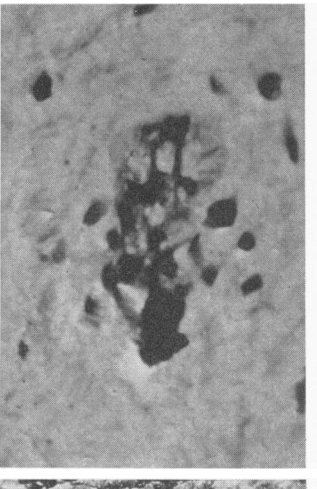

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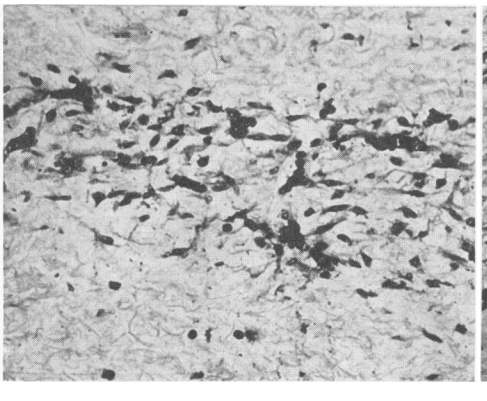

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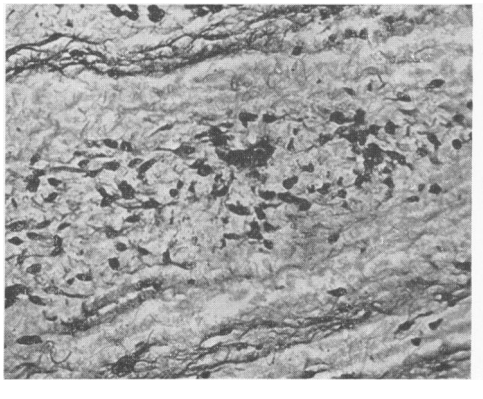

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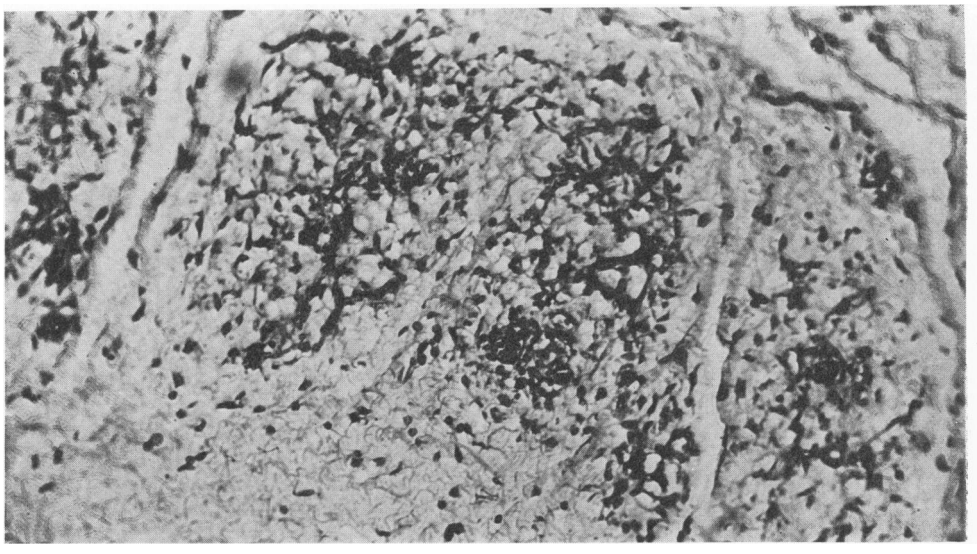
FIG. 6. Embryonal adipose tissue in the buccal fat pad of a 27 cm. fetus. Note the vascularity of the lobules. × 150.

FIG. 7. Adipose tissue in the buccal fat pad of a 23 cm. fetus. × 600.

FIG. 8. Adipose tissue in the perinephric region of a 28 cm. fetus. Note that it is not as well developed as that shown in Figure 7 from the buccal fat pad of a younger fetus. × 600.

FIG. 9. Axillary adipose tissue of a 41 cm. fetus. Cells contain multiple vacuoles separated by eosinophilic, granular cytoplasm. × 150.

FIG. 10. Adipose tissue in the perirenal region of a 48 cm. fetus. Many of the cells are multivacuolated, but the cytoplasm of a few is nonvacuolated and deeply eosinophilic. × 725.



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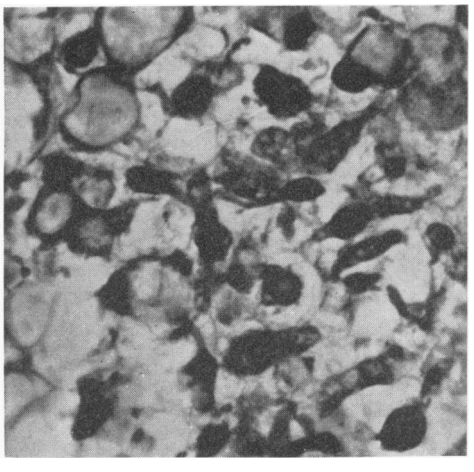

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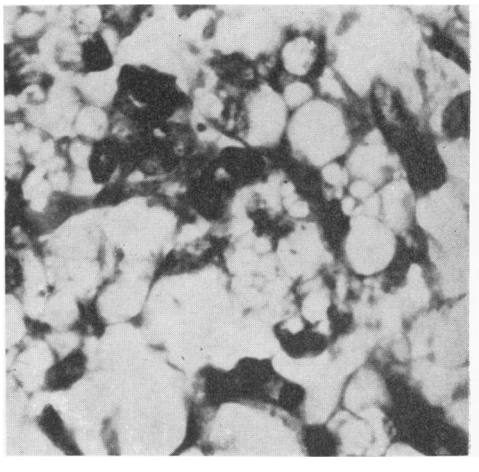

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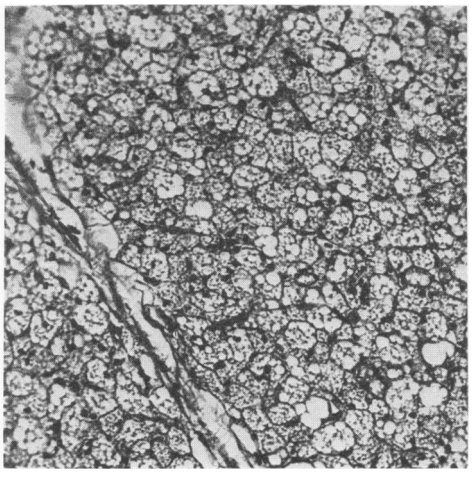

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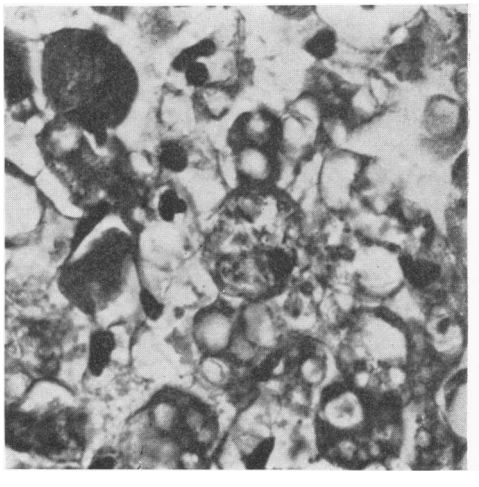

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