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Foamy Changes of Placental Cells in Fetal Storage Disorders

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Summary. Vacuolar cytoplasm in placental cells was observed in four cases. In each instance the baby was either stillborn or died soon after birth. One infant was shown to have Inclusion cell disease (Mucolipidosis II), whereas in the other cases biochemical studies were noncontributory or could not be carried out. The histologic changes of the placenta described in this report were restricted to the fetal elements and also included the X cells, providing further evidence that these cells are of fetal rather than maternal origin.

Introduction

Widespread vacuolar degeneration of certain tissues occurs in inherited disorders of metabolism such as generalized gangliosidosis (O'Brien, 1970), Hurler's disease (Haust and Landing, 1961), Sphingomyelin lipidosis (Niemann-Pick disease) (Baar and Hickmans, 1956), Glycolipid lipidosis (Fabry's disease) (Fredrickson and Irams, 1966). Vacuolation of syncytiotrophoblastic cells of the placenta was first described in Gm_1- gangliosidosis (Lowden *et al.*, 1973) and probably represented storage within the affected cells of ganglioside. In their case, the pathognomonic inclusions of Gm_1-gangliosidosis were demonstrated in fetal neurons. The marked solubility of the ganglioside in aqueous fixatives (O'Brien, 1970) may explain the absence of these inclusions from vacuolated placental cells. It is likely that placental vacuolation occurs in other inherited disorders in which specific products of metabolism accumulate to excess. Histologically recognizable lesions would thus have diagnostic significance either in confirming a prenatally diagnosed storage disorder or in alerting the pathologist to the presence of a clinically unrecognized defect. A recent review discussing the diagnosis of inherited metabolic disorders by study of amniotic fluid lists more than fifty diseases in which a prenatal diagnosis is possible (Seegmiller, 1974). The following report describes vacuolation within syncytiotrophoblastic tissue of four placentas encountered during routine histologic examination. In one of these cases the infant was found to have Inclusion cell disease (Mucolipidosis Type II). In each of the four cases foamy cytoplasmic changes were observed in syncytiotrophoblast, Hofbauer cells and X cells. In one autopsied infant a widespread storage disorder was identified microscopically.

Case I

Following an otherwise uneventful pregnancy, a 600 g stillborn fetus was born. The infant was not autopsied. Gross examination of the placenta showed no abnormalities but histologic sections revealed a foamy cytoplasmic change of syncytiotrophoblast, Hofbauer cells and X cells. The family history was noncontributory and this was her first pregnancy. The mother and father were tested for possible carrier status of Gm_1-gangliosidosis (Dr. David Wenger) and found to be normal in this respect. Placental tissue was initially fixed in formaldehyde. Subsequently it was placed in a 2.5% phosphate buffered glutaraldehyde, washed in phosphate buffer and postfixed in osmium tetraoxide. The tissue was then rinsed in distilled water, dehydrated in serial alcohols and embedded in Epon resin. When the blocks had hardened, 1 μ sections were cut, stained with methylene blue and examined by light microscopy. From appropriate blocks thin sections were made, stained with uranyl acetate and lead citrate and viewed on a Siemens Elmskop 101 operating at 80 kV. Paraffin-embedded hematoxylin and eosin stained sections showed foamy intracytoplasmic changes within trophoblastic cells, Hofbauer cells and X cells, but the cytoblasm of decidual cells retained its normal compact appearance. Moreover, amnion epithelium, endothelial cells, chorionic fibroblasts and umbilical cord were all normal. In the 1 μ thick Epon embedded sections the cytoplasm of trophoblastic cells (Fig. 1) and X cells (Fig. 2) contained innumerable large vacuoles. Ultrastructural examination showed that the vacuoles were generally translucent, containing occasional membranous inclusions resembling myelin figures. The number of vacuoles was usually sufficient to compress the nucleus giving it a scalloped appearance (Fig. 3).

Case II

A thirty year old gypsy was delivered of a premature female infant weighing 1700 g. This baby, however, had coarse features and abnormally short limbs with multiple fractures at birth. The infant had a heart murmur and developed hyaline membrane disease from which she died. Permission to autopsy was refused. The placenta weighed 500 g and was 17.0 cm in diameter. The umbilical cord was 5–6 mm in diameter but no other abnormalities were found. Two 3–5 mm nodules were present in the placenta which proved on light microscopic examination to be chorangiomas. The syncytial trophoblast had a foamy appearance and the syncytial cytoplasm was filled with fine vacuoles. These changes were also present in Hofbauer cells and X cells but were not observed in decidual cells. The appearance was entirely that seen in Case I. The possibility of Gm_1-gangliosidosis was excluded by the enzymatic studies (Table 1) which are very suggestive of Mucolipidosis II (I – cell disease) which also correlates with the clinical appearance. Electronmicroscopic studies of formalin-fixed placental tissue suggested the lysosomal nature of the vacuoles. O. H. P. who initially studied the placenta of this case had seen one previous similar placenta also from a gypsy mother. It was not further studied.

Case III

A 22 year old primipara gave birth to a stillborn macerated infant at 33 weeks of gestation. The umbilical cord was long and had coiled around the baby's neck. An autopsy was not

Fig. 1. Placental villi of Case I showing extensive cytoplasmic vacuolization of trophoblast and Hofbauer cells. (Epon, methylene blue × 650)

Fig. 2. Placental X-cells of case I with cytoplasmic vacuoles. (Epon, methylene blue × 1600)

Fig. 3. Portion of placental villus of Case I with intervillous space in top left corner. Cytoplasmic vacuolization of syncytium and particularly the Hofbauer cell at right. Note empty nature of vacuoles and scalloping of compressed nucleus. (Formalin tissue, postfixed, EM, uranyl acetate, lead citrate × 3000)

Fig. 4. Glomerulus of Case IV showing accumulation of distended, vacuolated cells presumed to be macrophages. (H and E × 650)

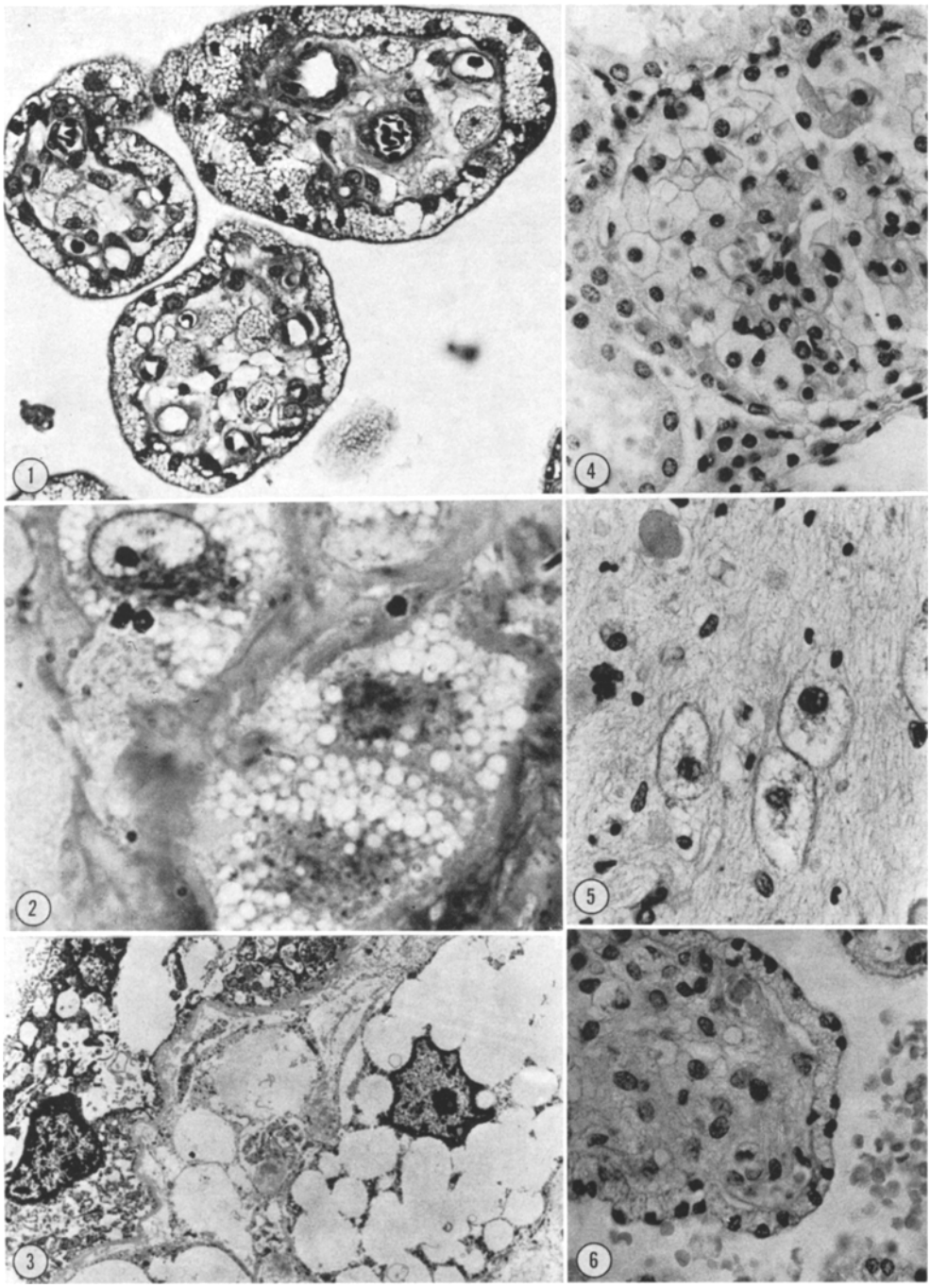

Fig. 5. Cerebral white matter of Case IV with calcification at left, distended and vacuolated glial cells in center and degenerated axon at top. (H and E×650)

Fig. 6. Placental villus of Case IV showing vacuolar changes similar to those in Fig. 1. (H and E×650)

Table 1

Serum:

Beta-galactosidase 242 μ Mol/ml/hr (50×normal)
Beta-glucuronidase 2,030 μ Mol/ml/hr (70×normal)
N-acetyl-beta-glucosaminidase 12,250 μ Mol/ml/hr (30×normal)

White blood cells:

Beta-galactosidase 93 μ Mol/mg protein/hr (moderately decreased)
Beta-glucuronidase 25.6 μ Mol/mg protein/hr (moderately decreased)
N-acetyl-beta-glucosaminidase 1,088 μ Mol/mg protein/hr (moderately decreased)

Table 2

White blood cells	μ Moles/mg Protein/hr Case IV	Control
Glucosyl ceramide beta-glucosidase	58.0	20.0
Sphingomyelinase	2.9	3.0
4 methylumbelliferyl beta-galactosidase	148.0	100.0
Galactosyl ceramide beta-galactosidase	5.7	4.7
Lactosyl ceramide beta-galactosidase	36.3	30.2
Hexosaminidase and % hexosaminidase A	normal	
Arylsulfatase A	70.0	67.0
Alpha-fucosidase	normal	

These studies were performed by Drs. S. Goodman and D. Wenger

performed. The placenta was pale, measured 14×17×3 cm and had similarly vacuolated foamy trophoblastic cells on microscopic examination. These showed no affinity for oil red 0 and PAS stains. No inborn errors are known to have occurred in the family and the mother has since given birth to two healthy infants.

Case IV

Severe ascites and peripheral edema were observed in a baby girl who was born to a 19 year old gravida 1 para 0 mother at 38 weeks gestation. The patient appeared cyanotic and was flaccid. Abdominal paracentesis produced 150 cc of fluid. Subsequent problems included respiratory distress, thrombocytopenia, a fracture of the right tibia and fibula and peritonitis. The child died at five weeks of age. There was evidence at autopsy of a storage disorder characterized by enlargement of liver and spleen and the presence of foamy vacuolar degeneration of cells in the reticuloendothelial system, liver, kidney (Fig. 4), pancreatic islets, thyroid, adrenal and in the central nervous system where neurons and glial cells were involved and axonal swelling and widespread calcium deposition were also noted (Fig. 5). The fixed brain was unusually firm. Anasarca was present with mesenteric lymphangiectasis. *Candida tropicalis* was cultured from blood and peritoneal fluid. Gross examination of the placenta at birth revealed no abnormalities but light microscopy showed generalized foamy intracytoplasmic changes in syncytiotrophoblast, Hofbauer cells and the X cells (Fig. 6). Electron-microscopic studies of brain and liver showed intracytoplasmic membrane bounded electron lucent vacuoles which did not contain any distinctive inclusions. The enzymatic studies performed are listed in Table 2. No significant enzyme abnormalities were found.

Discussion

In each of these four cases, abundantly vacuolated (foamy) cells were encountered in trophoblastic but not in decidual elements of the placenta. The exclusive involvement of fetal elements of the placenta suggests an inherited disorder of metabolism, however, a specific biochemical lesion could be demonstrated only in Case II. We are not aware of previous reports of placental histopathology in mucolipidosis Type II. The histologic findings, however, are similar to those reported in Gm_1-gangliosidosis (Lowden *et al.*, 1973) and placental lesions are said to exist in fetal Gaucher's disease (Ginsberg *et al.*, 1973) but their nature was not described. Gm_1-gangliosidosis was excluded indirectly in our Case I from the study of the parents, and this disorder as well as I-cell disease were excluded in CaseIV by enzymatic study of leukocytes. It would appear then that at least 3 and probably more metabolic errors can produce placental foamy changes that are indistinguishable one from another. Their identification rests on additional future enzyme studies. It is worth pointing out though that the placenta represents a gratuitous fetal biopsy capable of yielding morphologic and biochemical information about the fetus. It would be interesting to know whether the amniotic fluid would reflect these biochemical disorders for counseling purposes. Meanwhile the possibility of predicting recurrences in future pregnancies can be anticipated from placental needle biopsy.

Of additional interest in these cases is the presence of vacuolar changes in the X cells as well as in syncytiotrophoblast and Hofbauer cells. The X cells are polygonal cells with basophilic cytoplasm which are found in the placental septum, the basal plate, and in the walls of cysts (Ruffolo *et al.*, 1967). In the basal decidual floor, the X cells are enmeshed in fibrin and mingle with decidual cells. Scipiades and Burg described and named these cells in 1930 and there has been considerable debate as to whether they are of fetal or maternal origin (Boyd and Hamilton, 1970; Benirschke and Driscoll, 1967). Ultrastructural studies have been interpreted to suggest a maternal origin by some (Ruffolo *et al.*, 1967) and a fetal origin by others (Enders, 1968; Robertson and Warner, 1973; Maidman *et al.*, 1973). Recent studies of placentas obtained after delivery of male fetuses used quinacrine fluorescence to identify Y chromosomes in these cells and thus established their trophoblastic origin. The present cases provide further histologic confirmation of the fetal origin of these cells.

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References

Adachi, M., Schneck, L., Volk, B. W.: Ultrastructural studies of 7 cases of fetal Tay-Sachs disease. J. Neuropathol. exp. Neurol. **33**, 181 (1974)

Baar, H. S., Hickmans, E. M.: Cephalin lipidosis. A new disorder of metabolism. Acta med. scand. **155**, 49–64 (1956)

Benirschke, K., Driscoll, S. G.: The pathology of the human placenta, p. 203–215. Berlin-Heidelberg-New York: Springer 1967

Boyd, J. D., Hamilton, W. J.: The human placenta, p. 152–156, 182–188, 190–202. Cambridge: W. Heffer and Sons, Ltd. 1970

Enders, A. C.: Fine structure of anchoring villi of the human placenta. Amer. J. Anat. **122**, 419–452 (1968)

Fredrickson, D. S., Irams, E. G.: Ganglioside lipidosis: Tay-Sachs disease. In: The metabolic basis of inherited disease (Stanbury, J. B., Wyngaarden, J. B., and Fredrickson, D. S., eds.), 2nd ed., chap. 25, p. 523–538. New York: McGraw Hill 1966

Ginsburg, S. J., Groll, M.: Hydrops fetalis due to infantile Gaucher's disease. J. Pediat. **82**, 1046–1048 (1973)

Haust, M. D., Landing, B. H.: Histochemical studies in Hurler's disease: A new method for localization of acid mucopolysaccharide, and an analysis of lead acetate "fixation". J. Histochem. Cytochem. **9**, 79–86 (1961)

Lowden, J. A., Cutz, E., Conen, P. E., Rudd, N., Doran, T. A.: Prenatal diagnosis of Gm_1 gangliosidosis. New Engl. J. Med. **288**, 225–228 (1973)

Maidman, J. E., Thorpe, S. W., Harris, J. A., Wynn, R. M.: Fetal origin of X cells in human placental septa and basal plate. Obstet. Gynec. **41**, 547–552 (1973)

O'Brien, J. S.: Generalized gangliosidosis. In: Handbook of clinical neurology (Vinker, P. J., and Bruyn, G. W., eds.), vol. 10, chap. 19, p. 462–483. Amsterdam: North Holland Publishing Co.; New York: American Elsevier Publishing Co., Inc. 1970

Pompen, A. W. M., Ruitar, M., Wyers, H. J. G.: Angiokeratoma corporis diffusum (universale) Fabry, as a sign of an unknown disease; two autopsy reports. Acta med. scand. **128**, 234–255 (1947)

Robertson, W. B., Warner, W.: The ultrastructure of the human placental bed. J. Path. **112**, 203–211 (1974)

Ruffolo, R., Benirschke, K., Covington, H., Munro, A.: Electronmicroscopic study of the "X" cells in septal cysts of the human placenta. Amer. J. Obstet. Gynec. **99**, 1147–1159 (1967)

Scipiades, E., Burg, D.: Über die Morphologie der menschlichen Placenta mit besonderer Rücksicht auf unsere eigenen Studien. Arch. Gynäk. **141**, 577–619 (1930)

Seegmiller, J. E.: Amniotic fluid and cells in the diagnosis of genetic disorders. In: Amniotic fluid: Physiology, biochemistry and clinical chemistry (Natelson, S., Scommegna, A., Epstein, M., eds.), p. 291–316. New York: John Wiley and Sons 1974

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