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GM_1-gangliosidosis Type 1 Involving the Cutaneous Vascular Endothelial Cells in a Black Infant with Multiple Ectopic Mongolian Spots

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GM_1-gangliosidosis (GM_1) is one of the metabolic storage diseases, of which a differential diagnosis requires an array of biochemical assays to determine the enzyme deficiency. This approach is not only time-consuming and costly but also unavailable to most hospital laboratories. However, a presumptive diagnosis of GM_1 may be made on the basis of coarse facial feature, foamy endothelial cells in the cutaneous blood vessels and ectopic Mongolian spots, if present. A more definitive diagnosis of GM_1 is then made on the demonstration of deficiency of GM_1 β-galactosidase in leukocytes, plasma or cultured skin fibroblasts. Thus, a battery of enzyme tests may be averted. ***Key words: Infantile gangliosidosis type 1; Cutaneous vasculopathy – foamy endothelial cells.***

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Vacuolization of cutaneous vascular endothelial cells due to lipidosis is rare and has been seen in Fabry's disease (angiokeratoma corporis diffusum) (1, 2), fucosidosis (2) and GM_1-gangliosidosis type 1 (GM_1) (3, 4). It has also been reported that extensive and unusual Mongolian spots in black children are frequently associated with GM_1 (4–7). The combination of these findings may be pathonomonic of GM_1. We are presenting a case of a 13-month-old black female with such combined clinical manifestations, which led us to the presumptive diagnosis of GM_1. This impression was subsequently confirmed by a demonstration of low GM_1 β-galactosidase activities in leukocytes, plasma and cultured skin fibroblasts.

CASE REPORT

A black female infant was born to a single mother who contracted varicella during the first trimester. Pregnancy was otherwise unremarkable and the infant appeared normal at birth. She gained a few developmental milestones early and began to slow down by 6 months. She had problems with recurrent respiratory infections. At that time, she was thought to have fetal varicella syndrome. Physical examination at 13 months of age revealed a head circumference at the 70th percentile, coarse facies, protruding tongue with mild macroglossia and slightly claw-like fingers with spade-like thumbs. The liver was palpable 3 cm below the right costal margin. The spleen was not enlarged. The umbilicus was slightly protruding. There were bilateral nystagmus and right esotropia. The skin showed an 8-cm Mongolian spot over the sacrum and several 1–2 cm, gray-blue, oval macules with irregular feathery borders over the left and right scapular areas and middle back (Fig. 1a, b). According to her mother, the sacral spot was present at birth, but the others had developed gradually over the ensuing months. A routine blood examination demonstrated vacuolated lymphocytes on the peripheral blood smears. Blood aspartate aminotransferase level was 96 IU/L (normal, 5–35); urine acid mucopolysaccharides value was 33 mg glucuronic acid/g creatinine/24 hr (normal, 10–34). The presumptive diagnosis was lysosomal storage disorder, probably gangliosidosis type 1.

RESULTS

Light microscopy

The formalin-fixed, paraffin-embedded and H&E-stained sections of the skin biopsy obtained from a Mongolian spot revealed swollen capillary endothelial cells with pale, slightly

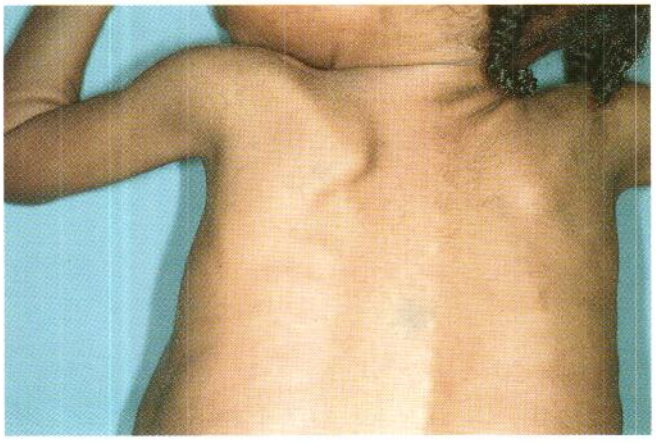

Fig. 1a. Photograph of grayish blue ectopic Mongolian spots over the right and left scapulae and vertebra T-8.

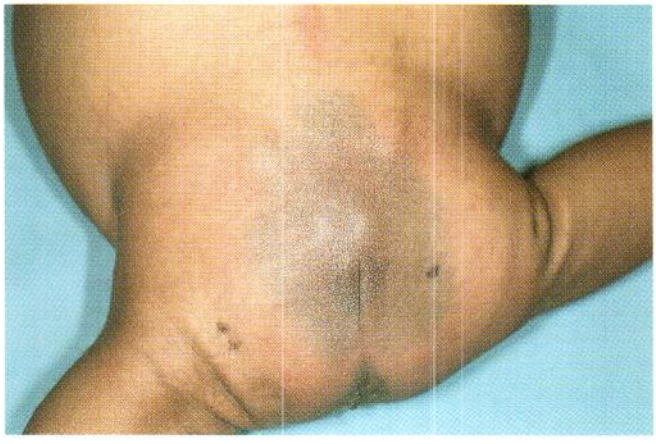

Fig. 1b. Photograph of the orthotopic Mongolian spot, about 8 cm in diameter, over the sacrococcyx.

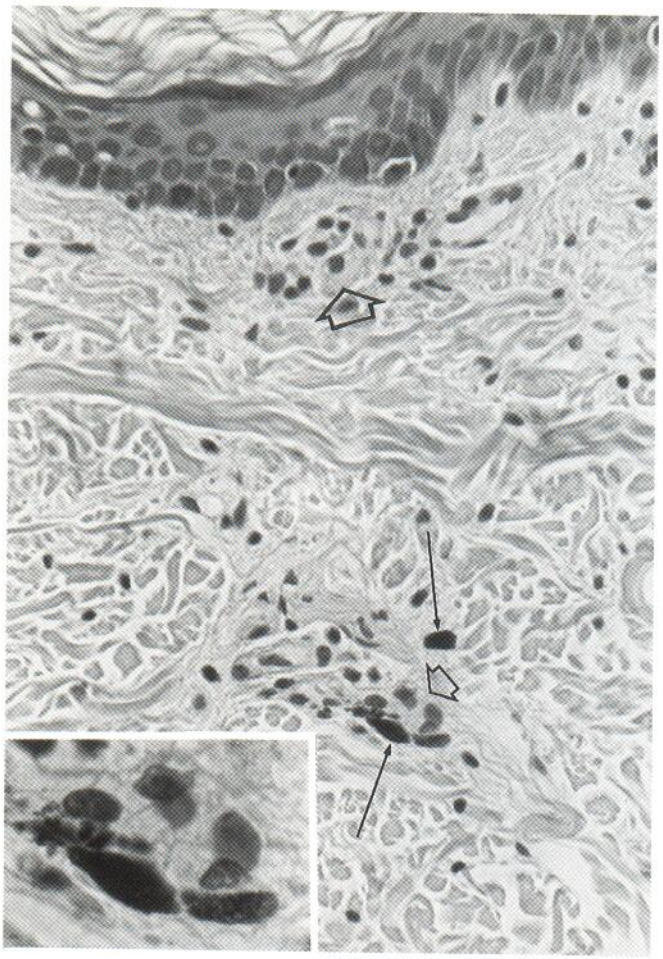

Fig. 2. Photomicrograph of the skin biopsy with Mongolian spot, showing fusiform and ovoid melanocytes (*solid arrows*) in the deep layer of dermis and capillaries with foamy endothelial cells (*open arrows*). H&E stain; original magnification, ×400. The inset depicts a fusiform melanocyte in the perivascular space of a capillary with foamy endothelial cells. H&E stain, ×1,000.

foamy cytoplasm. The vascular lumina were narrowed. Similar cytoplasm was also seen in the fibroblasts and secretory cells of eccrine glands. However on special stains, including PAS, luxol-fast blue, Alcian blue and toluidine blue, these pale cells were essentially negative. Melanocytes were scattered in the deep layer of dermis (Fig. 2). The epidermis, skin appendages and small nerve fibers were normal.

Electron microscopy

The endothelial cells of the dermal capillary were markedly enlarged with the vascular lumen narrowed. The cytoplasm was packed with numerous single-membraned vesicles, 450–900 nm in diameter, of which most were evacuated and clear, and some contained granules or round dense bodies, but no lamellated inclusions. The pericytes, fibroblasts and lymphocytes also displayed similar intracytoplasmic vacuoles. The melanocytes were rare and contained mature (stage IV) melanosomes (Fig. 3).

Enzyme assays

The enzyme profile assays were performed on leukocytes, plasma and fibroblasts from skin tissue culture in the laboratory of David A. Wenger, Ph.D., Division of Medical Genetics, Jefferson Medical College, Philadelphia. The results of individual enzyme activities are shown in Table I.

DISCUSSION

Vacuolated lymphocytes in the peripheral blood, if not artefactual, may represent a viral infection or leukemia/lymphoma. However, the aggregates of vacuoles in these cells without nuclear atypia are more suggestive of a storage disorder. Since children with glycogen storage disease tend to have a "doll face", the coarse facial features of this infant are more compatible with mucopolysaccharidoses and lipidoses/mucolipidoses (Hurler and Hurler-like syndromes). The former group of disorders may be excluded by the normal urine mucopolysaccharides and absence of Alder-Reilly bodies in the peripheral leukocytes. Among the latter group, Niemann-Pick and Tay-Sachs diseases were unlikely because the infant was not Jewish and, furthermore, these diseases usually spare the skin. Gaucher disease was unlikely because there was no splenomegaly. Additional possible diagnoses were Fabry's disease, fucosidosis, the mannosidoses, mucolipidoses and gangliosidoses. Differentiation of these metabolic disorders would require a profile of selected enzyme assays. However, the clinical features, findings of endothelial lipidosis in the cutaneous vessels and multiple ectopic Mongolian spots favored the diagnosis of gangliosidoses. A definitive diagnosis of GM_1-gangliosidosis type 1 was established by the low activities of GM_1 β-galactosidase in the leukocytes, plasma and skin fibroblasts.

Morphological study of skin biopsies has been considered helpful in the diagnosis of metabolic disorders. This case reinforces that general tenet.

Of the infants reported to date with GM_1-gangliosidosis and Mongolian spots, all have had the cutaneous lesions in atypical sites, and the lesions have been described as unusual, particularly with regard to their shape and feathery borders (4–7). In at least two infants, ours and the infant reported by Beattie & Harvey (6), the ectopic lesions were not present at birth but were of progressive onset during the early months of infancy and, once developed, remained fixed. Of the seven cases documented to date (including this case), five of the children were black and two were of Pakistani heritage. Only two had biopsies obtained from the unusual Mongolian spots. Both biopsy specimens showed scattered dermal melanocytes which had no inclusions or other abnormalities.

The association of extensive and ectopic Mongolian spots with gangliosidosis type 1 appears to be clinically significant rather than fortuitous, but there is no known biochemical basis for this concurrence. It is speculated that gangliosides could be ingested by the macrophages and inhibit their removing the melanocytic debris in the Mongolian spots, which normally fade away during early childhood; the lipid-laden lymphocytes, histiocytes and fibroblasts are unable to monitor the postnatal migration and wandering of dendritic cells and melanocytes; or the breakdown of the melanocytic debris is retarded by an enzyme deficiency analogous to and coincident

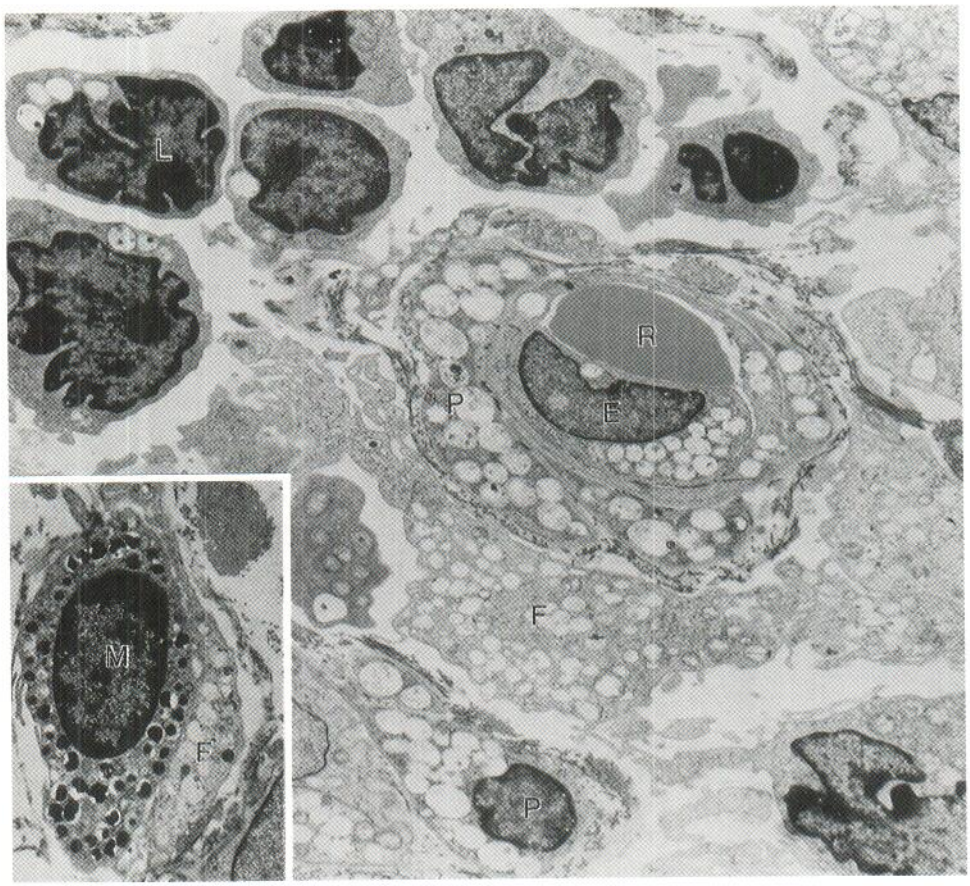

Fig. 3. Electronmicrograph of the skin biopsy, showing a capillary with a red blood cell (*R*) in the lumen and many vacuoles in the cytoplasms of endothelial cells (*E*), pericytes (*P*), fibroblasts (*F*) and lymphocytes (*L*). Original magnification, ×7,100. The inset depicts a dermal melanocyte (*M*) in association with a foamy fibroblast (*F*), ×7,100.

with that of gangliosidosis. However, the distribution of melanosis is much less diffuse than that of gangliosidosis.

The gangliosides have been demonstrated in cutaneous histiocytes, fibroblasts, pericytes and sweat glands, but their presence in vascular endothelial cells has more pathologic significance. These endothelial cells may become swollen and compress the vascular lumen with subsequent ischemia and thrombosis. Furthermore, vascular walls may be weakened and dilated, resulting in angiokeratoma and telangiectasia (8). A generalized vasculopathy may result in a multisystem disease.

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Table I. *Selected enzyme assays for mucopolysaccharidosis and lipidosis*

Units: Leukocytes and fibroblasts, nM/hr/mg protein; plasma, nM/hr/ml.

Abbreviations: 4MU = 4-methylumbelliferyl; MPS = mucopolysaccharidosis; NAc = N-acetyl; GM_1 = monosialoganglioside, number 1 on chromatography.

Interpretation: All enzymatic activities were normal except GM_1 β-galactosidase (normal ranges: leukocytes, 85–130; plasma, 8–40; fibroblasts, 200–600).

Diagnosis: GM_1-gangliosidosis.

Substrate	Enzyme	Disease	Leukocytes	Plasma	Fibroblasts
4MU-β-D-galactoside	β-galactosidase	GM_1-gangliosidosis	1.1	0.65	0.92
4MU-β-D-mannoside	β-mannosidase	β-mannosidosis	152.5	353.00	89.7
4MU-α-L-fucoside	α-L-fucosidase	Fucosidosis	48.4		
4MU-α-mannoside	α-mannosidase	α-mannosidosis	405.6		
4MU-β-D-glucuronidase	β-glucuronidase	MPS VII	387.4		
4MU-β-NAc glucosamine sulfate	β-hexosaminidase	Tay-Sachs disease and variants	448.0		538.5
4MU-α-L-iduronide	α-L-iduronidase	Hurler-Scheie disease	33.3		
Sialic acid content		Sialidosis, sialuria	29.8		
4MU-α-D-NAc glucosamine	α-glucosaminidase	Sanfilippo type B		46.70	

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