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Clinical, pathologic, and biochemical features of a cholesterol lipidosis accompanied by hyperlipidemia and xanthomas

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The coauthors would like to dedicate this publication to the memory of Michele R. Filling-Katz.

Article abstract—We describe the unique clinical and histopathologic features of a child with biochemical and immunocytochemical features of Niemann-Pick disease type C (NPC). Clinically, she was found to have multiple xanthomas of the upper aerodigestive tract with dysphagia and expressive language delay, splenomegaly, bony infarcts, and type IIb hyperlipidemia. Neurologic examination was otherwise normal. Microscopy revealed foam cells in her bone marrow, liver, tongue, tonsils, glottis, and in normal-appearing peritonsillar mucosa. Lipid analysis of a liver biopsy specimen showed a small increase in phospholipids, a twofold increase in sphingomyelin, a fivefold increase in cholesterol, and a marked (25-fold) increase in bis(monoacylglycerol) phosphate. Lysosomal acid hydrolase activities in cultured skin fibroblasts were nondiagnostic. Biochemical and immunocytochemical studies of cultured fibroblasts demonstrated lysosomal accumulation of unesterified LDL-derived cholesterol as well as delayed induction of homeostatic responses to endogenous cholesterol consistent with a diagnosis of NPC. Based upon these observations, we speculate that this patient could have a new phenotypic expression of NPC or represents a new cholesterol lipidosis biochemically resembling NPC. The chance occurrence of two separate lipid disorders seems less likely.

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Storage diseases are rare, recessive disorders involving the catabolism of amino acids, lipids, and carbohydrate-containing compounds. Manifestations of these storage diseases vary depending upon the substrate involved and the target organs affected. Elevations of plasma cholesterol and triglycerides are constant features of only a few storage diseases, most notably cholesterol ester storage disease and Niemann-Pick disease type B.¹⁻³ Xanthoma formation as a childhood feature of a lysosomal storage disease has been reported only in Farber's disease.⁴ Splenomegaly with or without hepatomegaly is a prominent feature of many of the sphingolipidoses as well as the glycogenoses. Splenomegaly also occurs in several other storage diseases, including Niemann-Pick disease type C (NPC), a metabolic disorder associated with a defect in intracellular transport of exogenously derived cholesterol.⁵⁻⁷ Bone

infarcts associated with lysosomal storage disease have only been reported in Gaucher's disease; bone pathology is an infrequent finding in other lysosomal storage diseases.

We report a child with a clinical syndrome of early onset of multifocal verruciform xanthomas (VX) of the aerodigestive tract, dysphagia, splenomegaly, liver, bone and bone marrow involvement, with biochemical and immunocytochemical features of NPC. We document profound visceral cholesterol, cholesterol ester, and phospholipid storage. To our knowledge, this is the first description of this unique combination of clinical findings.

Case report. *Clinical report.* The patient, now 80 months old, presented at age 18 months with splenomegaly detected by routine examination. A bone marrow biopsy at time of initial presentation revealed

* Deceased.

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Table 1. Fasting plasma lipid analysis

	Age	Chol	TG	VLDL	LDL	HDL	Apo A ₁	Apo B
Mother	27 yr	137	52	41	53	43		
Father	33 yr	237	222	57	145	35		
Patient	29 mo	343	339	71	254	18	99	99
	32 mo	340	270					
	51 mo	249	313			18		
	66 mo	236	202			28		
	77 mo	225	229			22		

Comparisons with normative data²² show that the patient's cholesterol (Chol), triglycerides (TG), very low-density lipoprotein (VLDL), and low-density lipoprotein (LDL) were elevated (greater than 95th percentile), while the patient's high-density lipoprotein (HDL) fell below the 5th percentile for her age group. Measurements of Apo A₁ and Apo B in the patient's plasma were within the normal range. The father's Chol, TG, and LDL were in the high-normal range, with low-normal HDL and an elevated VLDL. The patient's mother showed elevated VLDL with low LDL, normal levels of Chol and HDL, and a low-normal level of TG.

foamy macrophages, and blood analysis showed elevated SGOT and SGPT. A routine chest x-ray was unremarkable. Pregnancy was complicated only by vaginal spotting and cramping at 4 months. She was the only child of a healthy couple from Virginia with no history of consanguinity or lipid disorder. Their first child (female) was 5 years old and healthy.

At the age of 24 months (our first evaluation), she was further examined and her height was 80.5 cm (10th percentile), weight was 11 kg (10%), and head circumference was 40.5 cm (25%). Ophthalmologic examination was normal. Splenomegaly was confirmed by liver-spleen nuclear scan (liver 9 cm, spleen 11.5 cm; normals for age, 13 cm and 7 cm, respectively). Her fasting cholesterol and triglyceride levels (table 1) were found to be elevated, while a 2-D gel electrophoresis of apolipoproteins was unremarkable. The patient and both parents had dyslipidemias (table 1); however, the relationships of these dyslipidemias to the storage disorder in the patient is unknown at this time. Her karyotype was normal, and a lysosomal panel (obtained on fibroblasts) including acid lipase, ceramidase, and glucocerebrosidase was unrevealing except for a partial deficiency of sphingomyelinase. Five separate measurements of lysosomal sphingomyelinase (four in fibroblasts and one in leukocytes) gave the following values as percent of controls: 14%, 57%, 101%, and 68% (fibroblasts), and 188% (leukocytes). She was placed on a cholesterol- and triglyceride-restricted diet. Six months later, on this diet, her cholesterol and triglycerides were, respectively, 340 and 270 mg/dl. At the age of 29 months, a rapidly enlarging mass was detected on the posterior tongue (figure 1A). MRI studies of the neck and CT delineated the extent of the tongue tumor. CT of the chest revealed a significantly enlarged thymus for age but no evidence of interstitial lung disease. The mass (initially thought to be a papilloma) was interfering with speech and airway function and was removed at 29 months. At this time, a diagnostic bone marrow and a percutaneous liver biopsy were also performed (results described below). Formal developmental assessment (age 29 months) showed normal visual, gross motor skills, problem solving abilities, and receptive language development (Peabody Picture Language Test and Preschool Language Scale) but a deficit in expressive language.⁸ A postoperative assessment at 46 months demonstrated that verbal ability was now commensurate with chronological age. Her articulation remained highly unintelligible due to reduced tongue and lip strength and mobility, secondary to the xanthomatous lesions.

At 32 months, recurrent airway dysfunction, as evi-

denced by obstructive apnea, occurred secondary to adenotonsillar hypertrophy. These were removed as well as two new mucosal xanthomas of the tongue and supraglottic region. Two smaller xanthomas also noted were not removed. She was placed on 42 mg/kg/d of gemfibrozil in two divided doses at age 32 months and followed. Evaluation at 41 months revealed evidence of new xanthoma formation in her larynx and pharynx which did not threaten airway function, and minimal growth of the two existing xanthomas. A barium swallow revealed dysmotility and rigidity of the entire aerodigestive system.

At the age of 36 months, she developed an acutely swollen, painful, red, hot right ankle and refused to bear weight for 1 week. Erythrocyte sedimentation rate was normal. ASO titer, blood cultures, and rheumatoid factor were negative. A healing stress fracture in the third right metatarsal was seen on radiography. Her bones demonstrated demineralization throughout. A bone scan obtained the day after the complaint revealed increased uptake in the third metatarsal and decreased uptake in the calcaneus. Subsequent x-rays showed healing of the metatarsal and a subtle lucency of the calcaneus. She then developed two less severe episodes of significant pain that limited function, in the right foot and in the left wrist.

Methods. Tissue for electron microscopy was fixed in 2.5% glutaraldehyde in phosphate buffer (pH 7.4), post-fixed in OsO₄ and embedded in Maraglas 655 (Ladd Research Industries, Burlington, VT), stained with uranyl acetate-lead citrate, and examined with a Philips 400 electron microscope. Fibroblasts were obtained under approved diagnostic protocols. Fresh human low-density lipoprotein (LDL) in the density range of 1.019 to 1.063 g/ml and lipoprotein-deficient serum (<1.21 g/ml) (Meloy Laboratories, Springfield, VA) were prepared as previously described.^{5,9}

The primary antibody, rat monoclonal anti-human lysosomal membrane protein antibody, was supplied by Dr. J.W. Chen (Johns Hopkins University, Baltimore, MD). The secondary antibody, affinity-purified goat anti-rat IgG rhodamine-conjugated antibody, was purchased from Jackson Laboratories, Avondale, PA, and filipin was purchased from Sigma.

Fresh tissue samples (15 to 100 mg) were mechanically homogenized in 500 μ l of water. After removal of an aliquot for protein determination¹⁰ quantitated relative to serum albumin, lipid analyses were performed on chloroform-methanol (2:1 v/v) extracts of homogenized tissue

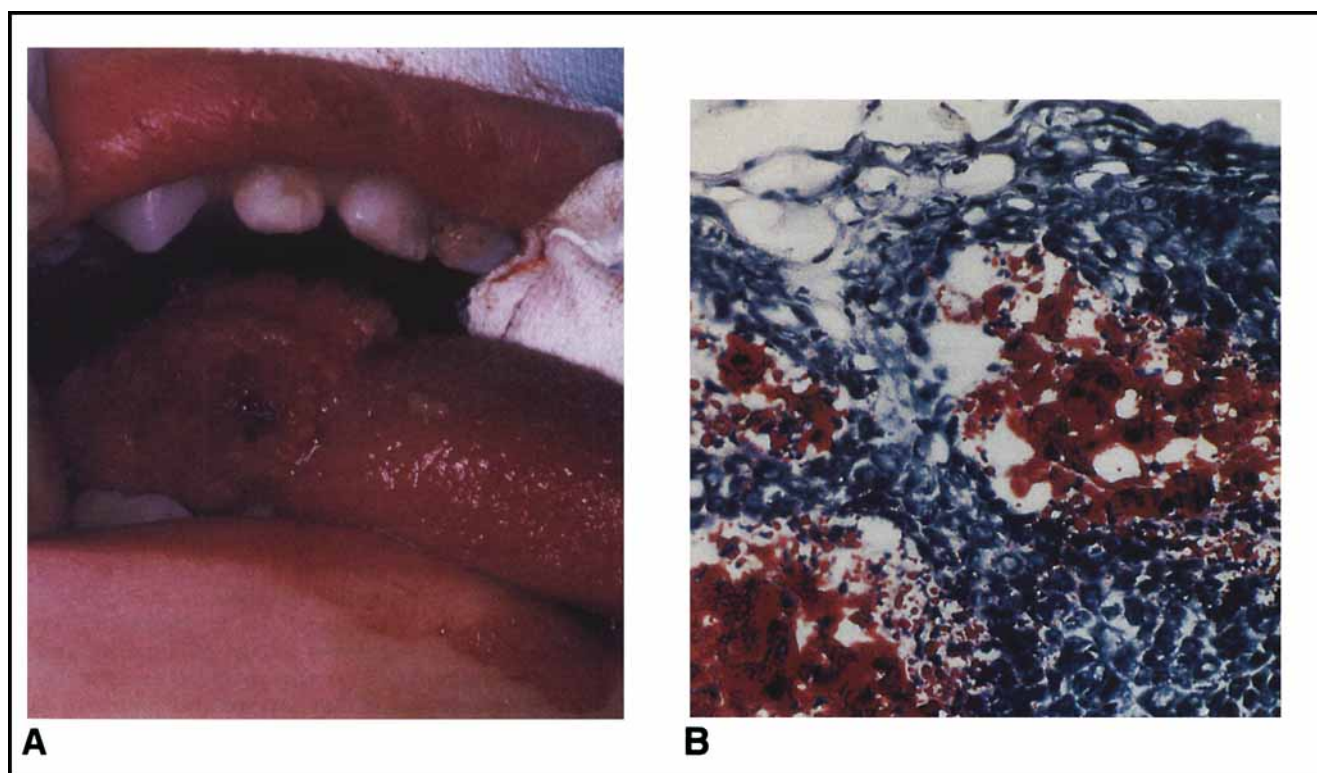


Figure 1. (A) Clinical photograph of tongue showing large verruciform mass lesion occupying one third of the base of the tongue. (B) Photomicrograph of the tongue verruciform xanthoma demonstrating marked red staining of lipid within the cytoplasm of submucosal xanthoma cells (Oil-Red O stain, $\times 125$ before 8% reduction).

as previously described.¹¹ Thin-layer chromatography (TLC) on silica plates (20 cm \times 20 cm \times 0.25 mm; E. Merck) used the following solvent systems: system A, hexane/diethyl ether/glacial acetic acid (80:20:1) for neutral lipids; and system B, chloroform/methanol/glacial acetic acid/water (60:40:4:2) or system C, chloroform/methanol/29% ammonium hydroxide (65:35:5) for phospholipids,¹² and were developed as described. Response curves were derived from commercial lipid standards (Avanti Polar Lipid Inc) for each TLC plate. Bis(monooacylglycerol) phosphate (BMAGP) was determined relative to the phosphatidyl ethanolamine response curves because of unavailability of suitable standards.

Cellular cholesterol processing in cultured fibroblasts in the presence and absence of LDL and the subsequent quantitation of cholesterol mass and cholesterol esterification were carried out as previously described.^{5,6}

A Leitz fluorescence microscope with excitation filters BP-350-410 for filipin and BP-530-560 for rhodamine was used for the immunocytochemical studies. Cells for fluorescent cytochemical (filipin) and immunocytochemical (rhodamine) staining were maintained, harvested, and then seeded according to methods published previously, and were viewed at 48 hours.⁷

Results. Lipid analysis of the liver biopsy specimen from the patient (table 2) was similar to previously obtained specimens from NPC patients in that cholesterol was elevated (five-fold), and a modest elevation was found in sphingomyelin (two-fold). BMAGP, moreover, was significantly increased relative to the virtually undetectable levels in normal liver.¹³⁻¹⁵

The lipid analysis of the initial tongue lesion from this patient relative to an age-matched autopsy normal tongue specimen is found in table 2. Cholesterol ester was more than 10-fold elevated. Triglycerides were 20-fold decreased in the xanthoma tissue over normal tongue tissue controls. Cholesterol, sphingomyelin, and phosphatidyl choline were all mildly increased.

Cholesterol esterification was quantitatively measured (table 3) at 6 hours and 24 hours relative to normal-derived, NPC-derived, and patient-derived cultured skin fibroblasts. The defect in esterification of exogenous cholesterol demonstrated by our patient's fibroblasts is qualitatively similar to the NPC fibroblasts. Cholesterol mass measurements following LDL-coculture (table 3) do not demonstrate any evidence for defective receptor-mediated uptake.

Cytochemical analysis of the patient's fibroblasts following 48 hours of LDL uptake revealed extensive filipin-cholesterol staining in the perinuclear region (figure 2C) which colocalizes with the lysosomes (figure 2D). In normal cells, cholesterol does not accumulate in lysosomes (figure 2, A and B). This abnormal storage and accumulation of exogenously derived cholesterol is a hallmark of NPC.

The pathology of lesions in the aerodigestive tract (figure 1) consisted of multifocal submucosal accumulation of foamy macrophages which in the tongue was accompanied by marked epithelial hyperplasia causing a VX.¹⁶ The foamy macrophages were dis-

Table 2. Lipid analysis of liver biopsy and tongue xanthoma

Lipid	Sample	Lipid concentrations (mg lipid/g wet wt)			Normal tongue control
		Patient liver	Normal liver*	Patient xanthoma	
Cholesterol		15.0 ± 2.2†	2.9 ± 0.9	2.5 ± 0.3†	1.4 ± 0.1
Cholesterol ester		6.9 ± 0.9†	0.98 ± 0.5	3.6 ± 0.6†	0.18 ± 0.09
Sphingomyelin		3.8 ± 0.4†	1.8 ± 0.6	1.5 ± 0.1†	0.70 ± 0.03
BMAGP		6.5 ± 0.2†	0.18 ± 0.1‡	ND	ND
Phosphatidylcholine		16.0 ± 0.7	10.7 ± 2.2	4.8 ± 0.3†	3.2 ± 0.3
Phosphatidylethanolamine		7.5 ± 0.4	6.4 ± 1.2	2.8 ± 0.5	1.9 ± 0.4
Phosphatidylinositol		3.4 ± 0.2	2.4 ± 1.2	0.57 ± 0.08	0.35 ± 0.04
Phosphatidylserine		1.7 ± 0.2	1.9 ± 0.95	0.84 ± 0.01	0.61 ± 0.2
Triglycerides		4.3 ± 0.4	19.0 ± 16.0	0.88 ± 0.2†	21.0 ± 3.0
Free fatty acids		0.3 ± 0.06	Not reported	0.58 ± 0.09	0.50 ± 0.2

* Data of Kwiterovich et al.²³
† Highly significant differences ($p < 0.01$ in a two-tailed Student's t test) between patient tissue and normal controls.
‡ Data of Yamamoto et al.¹⁵
BMAGP Bis(monoacylglycerol) phosphate.
ND Not detected.

Lipid analyses were performed by thin-layer chromatography with scanning densitometry as described in Methods. Bis(monoacylglycerol) phosphate was quantitated relative to phosphatidylethanolamine standards. Lipid concentrations are given as mean of 2-3 measurements ± 1 SD. Protein contents (mg/g wet wt, N = 4) were: patient liver, 124 ± 11; patient xanthoma, 120 ± 10; normal tongue control, 92 ± 2.

Table 3. Cellular uptake and processing of LDL by cultured fibroblasts

Cell type	LDL culture (50 µg/ml)	Cellular responses		
		Cholesterol levels (nmol/mg protein)		Cholesterol [³ H]-oleate synthesis (nmol/mg prot/time interval)
		Free	Esterified	
Normal	---	50	0	0.05/6 hr
Patient	---	36	0	0.08/6 hr
NPC	---	44	0	0.06/6 hr
Normal	6 hr	73	15	3.3/6 hr
Patient	6 hr	63	0	0.10/6 hr
NPC	6 hr	74	5	0.05/6 hr
Normal	24 hr	92	54	57.6/24 hr
Patient	24 hr	115	13	4.2/24 hr
NPC	24 hr	167	9	0.8/24 hr

The masses of cholesterol and cholesterol ester that were accumulated during LDL loading were measured by enzymatic assays using cholesterol oxidase and cholesterol esterase/cholesterol oxidase, respectively.⁵ The rate of cholesterol ester synthesis was determined by including [³H]-oleate in the tissue culture media throughout the LDL loading period, or for 6 hours in the absence of LDL.⁶ The processing of LDL-derived cholesterol was abnormal in the patient's fibroblasts as seen by significant deficiencies of both the synthesis and accumulation of cholesterol esters in comparison with normal cells. Similar deficiencies were seen in a documented NPC fibroblast line.

tended by abundant lipid deposits which stained positively with the Oil-Red O stain (figure 1B).

Selective biopsy of normal-appearing tonsillar mucosa also revealed pathologic evidence of lipid deposition in the cytoplasm. Electron microscopic analysis of the VX as well as surrounding normal-appearing tongue and tonsillar tissue shows the lipid deposition to be in both the cytosolic and lysosomal compartments (figure 3A). Lipid deposition in the cytosol of endothelial cells was also observed (figure 3B). Rare cholesterol clefts were observed in macrophages as well.

The liver biopsy (figure 4) showed substantial

lipid accumulation in both hepatocytes and Kupffer's cells. Mild hepatic fibrosis was additionally observed. Electron microscopy of the liver showed the presence of whorled myelin figures in Kupffer's cells and hepatocytes. Cholesterol cleft formation was also observed in hepatocytes. Several types of membrane-bound vesicles were observed in addition to coarse granular material within the cytosol. Foam cells were also present in the bone marrow aspirate.

Discussion. The combination of clinical, pathologic, biochemical, and immunocytochemical features appear to be unique to this patient, although the individual findings overlap with the features of NPC, Farber's disease, and cholesterol ester storage disease. Clinically, the patient manifests a systemic disorder of childhood onset with multifocal VX throughout the aerodigestive tract, splenomegaly, enlarged thymus and tonsils, with osteopenia, bony fracture and infarction, and a type IIB hyperlipidemia. The tongue xanthoma obstructed airway function and impaired expressive speech. Both problems are improving following surgery. We empirically treated our patient with gemfibrozil in hopes of arresting xanthoma growth and believe that we may have delayed the continued growth of the xanthomas as well as treated the hyperlipidemia. The xanthomas have not required removal over the past 2-year follow-up, although growth has occurred. Splenomegaly was not symptomatic in our patient but is common in NPC^{17,18} and in many other storage disorders. Osteopenia and bony infarction, both present in our patient, are not primary clinical features of NPC. Asymptomatic osteopenia may be seen in most type A and some type B Niemann-Pick dis-

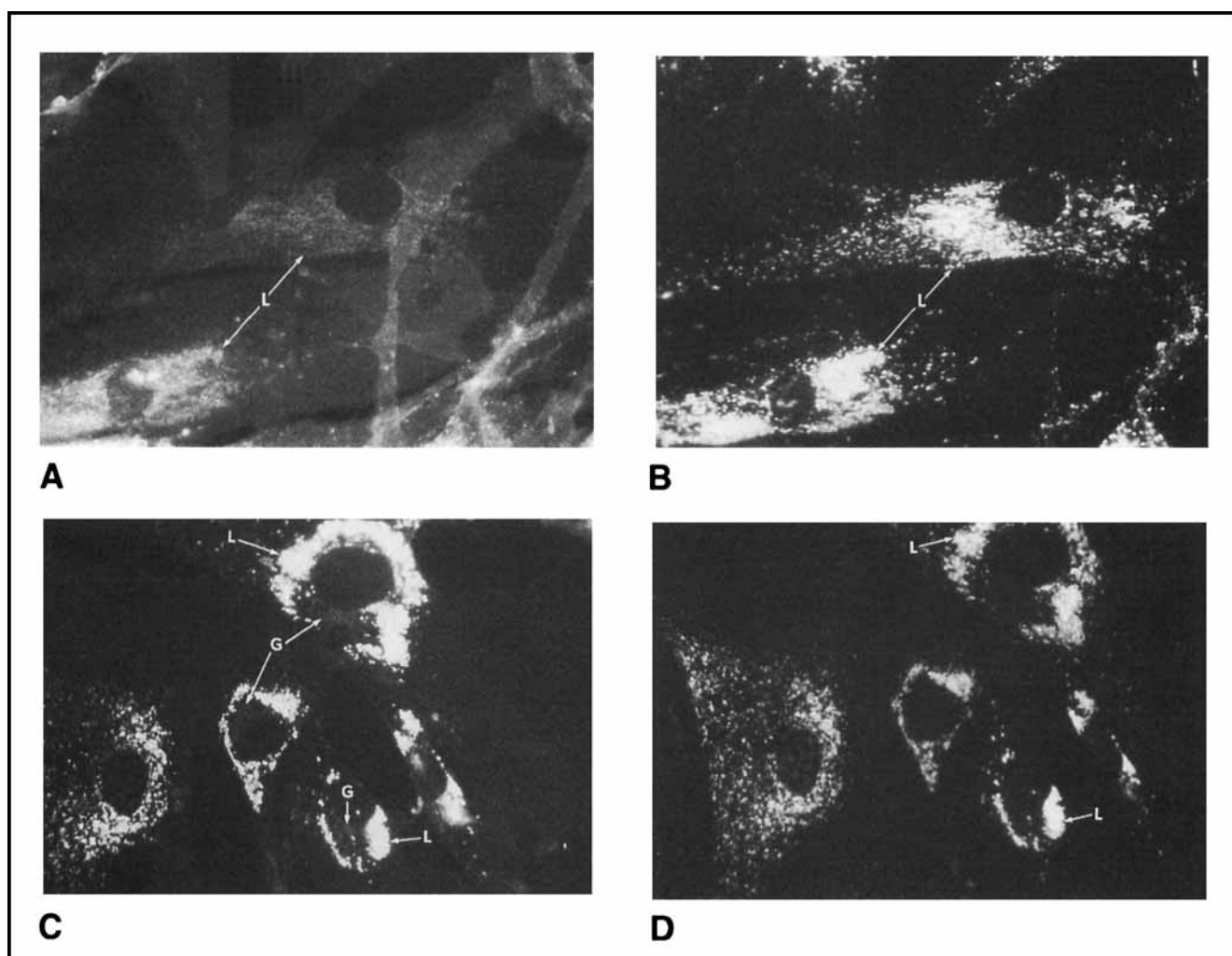


Figure 2. (A and B) Normal fibroblasts incubated with LDL for 48 hours and stained with filipin to locate unesterified cholesterol (A) or immunostained with antibody to lysosomal membrane protein to identify lysosomes (B-L). A faint filipin-cholesterol fluorescence (A) colocalizes with lysosomal immunofluorescence (B). $\times 625$ before 50% reduction. (C and D) Patient fibroblasts incubated with LDL for 48 hours and stained with filipin to locate unesterified cholesterol (C) or antibody to lysosomal membrane protein to identify lysosomes (D-L). An intense filipin-cholesterol fluorescence (C) colocalizes with lysosomal immunofluorescence (D). There is also filipin-cholesterol fluorescence associated with the Golgi complex (C-G). $\times 625$ before 50% reduction.

ease patients.¹⁹ We are aware that the profound lipid infiltration of the aerodigestive tract is unique to this patient. Lipid infiltration of the aerodigestive tract has been reported in a patient with xanthomatosis disseminatum with diabetes insipidus and one other normolipemic adult patient²⁰ but has not occurred in any NPC patient. The patient's young age precludes determining whether neurologic sequelae (an integral part of NPC¹⁷) will be a part of our patient's disorder. Lack of either vertical saccadic or pursuit eye movement abnormalities would be very unusual in an NPC patient¹⁸ but has been previously observed by us once after screening at-risk siblings (unpublished observation).

We reviewed the unusual pathologic nature of the aerodigestive tract VX elsewhere.¹⁶ New xanthomas of the patient's aerodigestive tract have continued to develop over a several-year follow-up period, and pathologically we observed evidence of diffuse lipid deposition even in normal-appearing

aerodigestive mucosa. Viscera and marrow tissues from this unique patient also demonstrate pathologic evidence of lipid accumulation in lysosomes. An analysis of hepatic tissue shows features reminiscent of NPC including elevation of cholesterol, sphingomyelin, and BMAGP.¹⁴ This minor phospholipid is present in very low concentrations in normal tissues and accumulates in a subset of lysosomal storage diseases.¹³⁻¹⁵ The elevation of hepatic cholesterol ester storage and the presence of cholesterol clefts in our patient are not prominent features in NPC. Neither is the extent of cholesterol ester accumulation consistent with cholesterol ester storage disease.^{1,21}

The lipid analyses of the oral VX, compared with analyses in a control autopsy specimen and in a xanthoma from a type V hyperlipidemic patient,²⁰ reveal several unique biochemical abnormalities. These abnormalities may be relevant in that biopsied normal-appearing mucosa in this child also

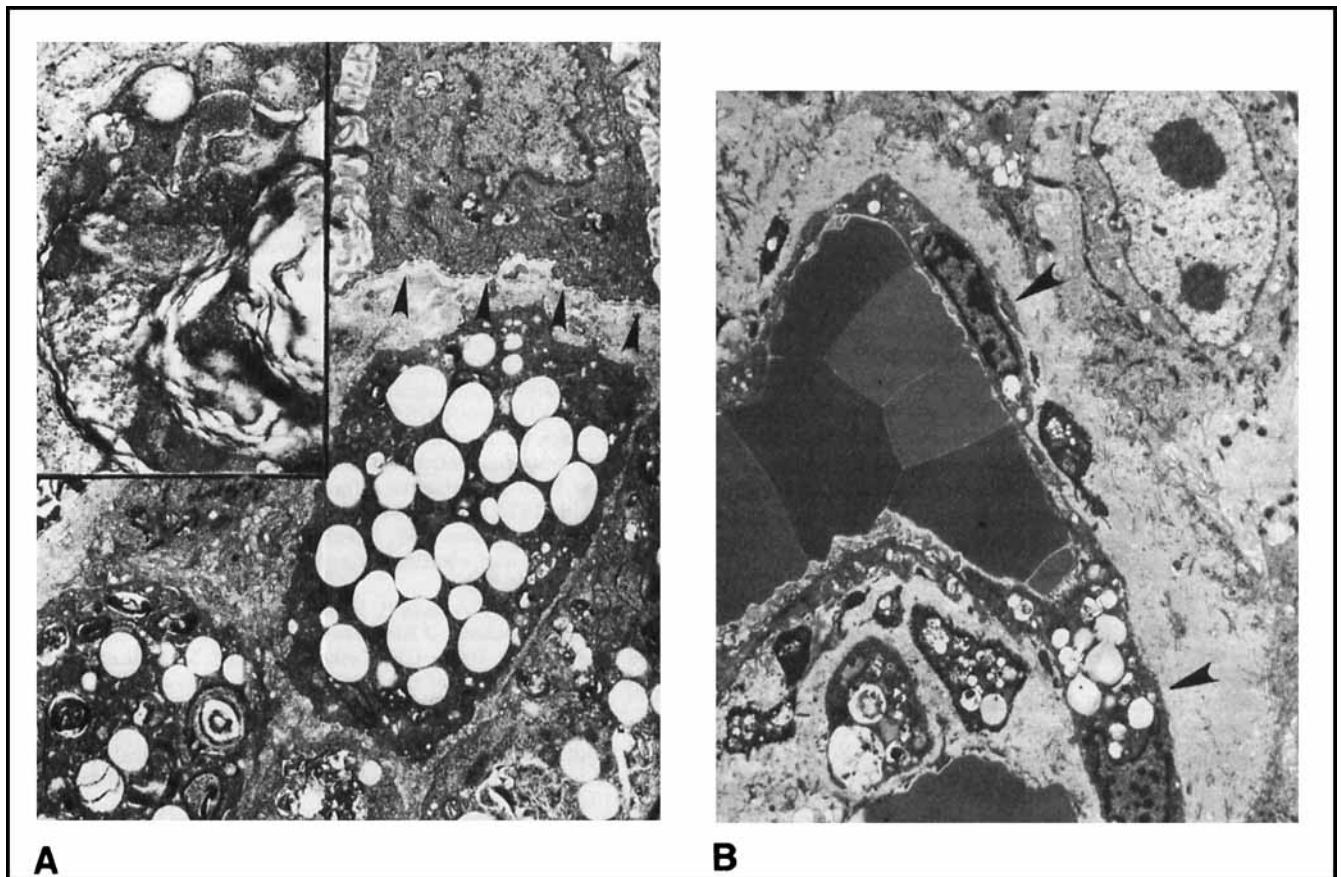


Figure 3. (A) Electron micrograph from verruciform xanthoma showing cells in the submucosa filled with lipid droplets. The overlying epithelial cells are separated from the submucosa by basal lamina (arrowheads). The lipid droplets are seen primarily in the cytosol, but also in tertiary lysosomes, mixed with myelin figures (inset). (Uranyl acetate/lead citrate, $\times 6800$ before 17% reduction, inset $\times 38500$ before 17% reduction.) (B) The endothelial cells (marked by arrowheads) lining the capillary lumen in the xanthomatous lesion contain intracytoplasmic lipid droplets (uranyl acetate/lead citrate, $\times 3900$ before 17% reduction).

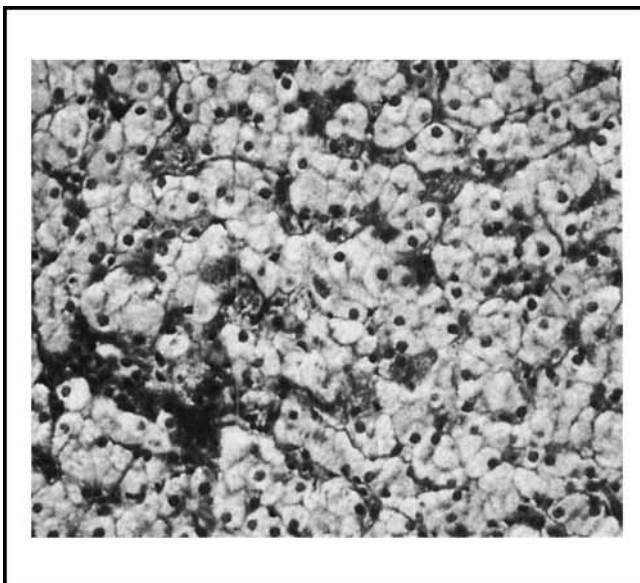


Figure 4. Photomicrograph of liver with diastase digestion shows focal positive staining of hepatocytes as well as Kupffer's cells (periodic acid-Schiff stain with diastase digestion, $\times 200$ before 26% reduction).

showed histologic evidence of lipid accumulation. In the xanthoma, the triglyceride content was very low. There were significant elevations in the amounts of cholesterol ester, phosphatidyl choline, and phosphatidyl ethanolamine in this patient's xanthoma over those described in previous reports of lipid analysis in xanthoma tissue.²⁰ We also noted other minor differences in the lipid composition. Clearly, the biochemical composition of this young patient's xanthoma differs from the lipid composition obtained in other types of patients, lending further evidence to the uniqueness of this patient.

The cellular processing of cholesterol in fibroblasts cultured with LDL was shown to be defective in this patient. The defect appears to closely resemble the unique lesion in cholesterol metabolism reported to be associated with NPC. In this disease, as well as with the present patient, uptake of LDL-cholesterol by cultured cells is associated with excessive accumulation of unesterified cholesterol.

Since the precise etiology of NPC has not yet been determined on a molecular basis, it is difficult to ascertain the etiology of the unique clinical fea-

tures of this patient. They could represent the clinical expression of a phenotypic variant of NPC or the combination of another lipid storage disorder in an NPC patient with the consequent unique clinical features. Alternatively, the patient might have a biochemical phenocopy based on a different genetic defect perhaps involving regulation of some of the same metabolic pathways. Complementation studies with NPC patients may help in determining whether or not this disorder is allelic to that of the NPC mutation. Further delineation will await discovery of the molecular basis of NPC.

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