Autopsy Pathology of Infantile Neurovisceral ASMD (Niemann-Pick Disease Type A): Clinicopathologic Correlations of a Case Report and Review of the Literature

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Introduction

Acid sphingomyelinase deficiency (ASMD; commonly known as Niemann-Pick Disease [NPD] A and B) is a rare lysosomal storage disorder characterized by the pathological accumulation of sphingomyelin, particularly in cells within the liver, spleen, lungs, and bone marrow, leading to significant clinical disease. The infantile neurovisceral (Niemann-Pick Disease type A; NPD A) form of the disease is characterized by visceral and severe neurodegenerative involvement with death in early childhood. We report the clinical course and corresponding autopsy findings in a case of a 3 year old male patient with infantile neurovisceral ASMD. The patient presented with difficulty feeding during the first 3 months of life. Repeated medical examinations revealed reflux, mildly enlarged liver and spleen, and elevated liver function tests. At 7 months of age, a diagnosis of NPD A was made based on liver biopsy examination, undetectable acid sphingomyelinase enzyme activity, and genetic testing. A complicated clinical course resulting from multisystemic disease, including the CNS, developed over the next 2.5 years. The patient passed away at the age of 3 years 2 months from complications of the disease. A full autopsy was performed at the request of the parents. Tissue from the autopsy was donated to Sanofi Genzyme by the Wylder Nation Foundation and with the informed consent of the parents. A comprehensive examination of the autopsy tissue was conducted including routine paraffin processing and staining, high resolution light microscopy, staining for sphingomyelin, and electron microscopy, along with a review of the patient's medical record. We report the clinicopathologic correlations of these findings and discuss the relevance of these results to the clinical practice of physicians following patients with ASMD.

Methods

We received representative organ samples from a complete autopsy. A portion of each sample was fixed in 10% NBF, processed into paraffin blocks, sectioned, and stained with routine hematoxylin and eosin or trichrome stain. A separate portion of each sample was fixed in 2% glutaraldehyde/2% paraformaldehyde in 0.2 M sodium cacodylate buffer, pH 7.3, and processed into epon blocks for high resolution light microscopy and electron microscopy as previously described[1]. The tissue was donated to Sanofi Genzyme for research purposed by the Wylder Nation Foundation. Both parents of the deceased provided full consent to the donation to further research into this rare disease.

Clinical Course

The patient was a three year old male child who was diagnosed with Infantile Neurovisceral ASMD (NPD A).

- The patient presented at birth with mild jaundice and dysphagia.
- Age 3 months: Signs of reflux, poor weight gain, and a small abdominal wall hernia became apparent. An ultrasound revealed enlargement of liver and spleen. Liver function tests were elevated.
- Age 7 months: A liver biopsy was performed. Pathology showed foam cells suggestive of a lysosomal storage disorder. Subsequent enzyme and genetic testing pointed to a diagnosis of Infantile Neurovisceral ASMD. The patient's ASM levels were undetectable.
- Age 9 months: Evaluation of the patient suggested CNS involvement. Evaluated for possible stem cell treatment but family declined. Daily physical, occupational, and feeding therapy at home was initiated.
- Age 12 months: The patient continued to have feeding difficulties and at 16 months the patient underwent cholecystectomy (dx: chronic cholecystitis/cholelithiasis) and G-tube placement.
- Age 17 months: Begins b.i.d. treatment with albuterol/Pulmacort for breathing difficulties.
- Age 19 months: Parents notice behavioral changes. The patient was diagnosed with hydrocephalus and a VP shunt is placed.
- Age 21 months: An echocardiogram showed tricuspid and mitral valve regurgitation. Abdominal ultrasound showed diffuse fatty infiltration of the liver.
- Age 23 months: Increased feeding difficulty with frequent vomiting. Patient placed on total parenteral nutrition (TPN). Development of severe ascites (800cc); placement of catheter for continuous abdominal fluid draining. Shunt converted to VA shunt.
- Age 30 months: Hypernatremia diagnosed during a hospitalization.
- Age 35 months: Patient hospitalized and treated for pneumonia.
- Age 37 months: Surgery to remove a growth on the patient's right ankle, diagnosed as a hemangioma.
- Age 38 months: The patient passes away peacefully at home.

Findings at Autopsy

- The sphingomyelin present in the neurons of the cortex and brainstem is consistent with CNS clinical observations. The findings in the brainstem along with the sphingomyelin accumulation present in skeletal myocytes of the tongue and fibroblasts and myocytes around the trachea are also likely contributors to the patient's dysphagia.
- Grossly, the heart was enlarged with concentric left ventricular hypertrophy. This is consistent with the finding of sphingomyelin accumulation in cardiomyocytes at the microscopic level.
- The patient's clinical pneumonia is consistent with the gross congestion, edema, and consolidation observed at autopsy, which correlates with the massive infiltration of the airspaces by sphingomyelin-engorged macrophages, microscopically.
- Hepatocytes and Kupffer cells were engorged with foamy material throughout. Portal-portal and portal-central bridging fibrosis and nodule formation on pathology is consistent with cirrhosis, elevated LFTs, and the development of abdominal ascites.
- The spleen was filled with macrophages engorged with sphingomyelin, consistent with the patient's splenomegaly.
- Involvement of the kidney and adrenal by massive cellular accumulation of sphingomyelin may have been contributors to the patient's hypernatremia diagnosed during a hospital admission at age 30 months.
- Involvement of the exocrine pancreas may have been a contributor to poor weight gain.

Results

Organ	Cells containing sphingomyelin
Brain: cortex	Neurons, capillary endothelial cells, pericytes
Brainstem	Neurons
Tongue	Skeletal myocytes
Trachea	Fibroblasts in surrounding connective tissue, myocytes
Thyroid	Follicular epithelial cells
Lung	Alveolar macrophages, bronchiolar epithelium
Heart	Cardiomyocytes, capillary endothelial cells, vascular smooth muscle cells
Aorta	Vascular smooth muscle cells
Esophagus	Endothelial cells of capillaries and lymphatics, macrophages within the lamina propria; smooth muscle cells of the muscularis propria
Small intestine	Ganglion cells of myenteric plexus (Auerbach's), vascular smooth muscle cells, smooth muscle cells of the muscularis externa
Liver	Hepatocytes and Kupffer cells presented with an enlarged, foamy appearance, suggestive of sphingomyelin accumulation. The liver appeared cirrhotic on trichrome stained sections with dense bridging bands of fibrosis throughout the section. Clusters of foamy macrophages with pericellular fibrosis appeared throughout the field, particularly around portal triads.
Spleen	Splenic macrophages, vascular endothelial cells
Lymph nodes	Macrophages
Bone marrow	Bone marrow cavity filled with engorged Niemann Pick cells
Pancreas	Acinar cells of exocrine pancreas; much less in endocrine pancreas islet cells
Adrenal	All cells in all zones of the cortex; no medulla present
Kidney	Proximal tubular epithelium, Bowman's capsule, podocytes, mesangial cells
Skeletal muscle	Small amounts in skeletal myocytes, perinuclear location

Table 1: Sphingomyelin accumulation was present in the cells of multiple organs

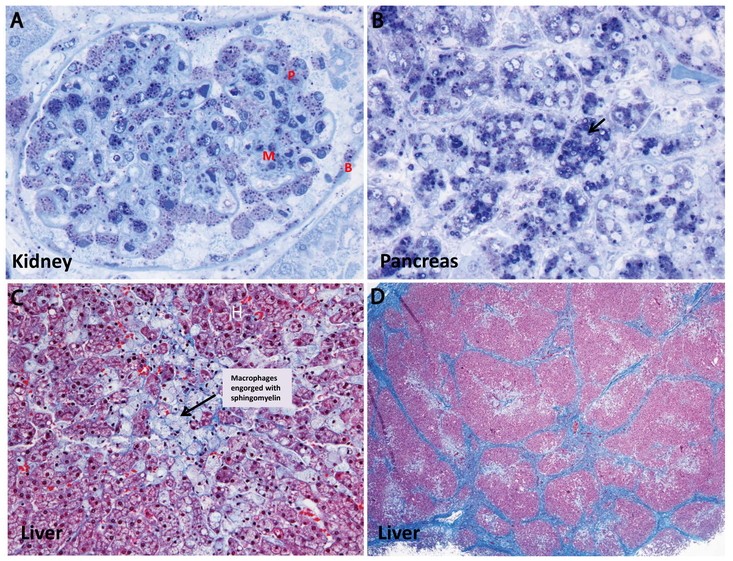

Figure 2: Sphingomyelin accumulation was present in the kidney, pancreas and liver. A. Sphingomyelin is present in numerous cell types within the renal glomerulus including podocytes (P), mesangial cells (M), and lining cells of Bowman's capsule (B) (1 micron epoxy resin section, modified toluidene blue stain, 600x). B. The cells of the exocrine pancreas are also heavily laden with accumulated substrate. (1 micron epoxy resin section, modified toluidene blue stain, 600x). C. In paraffin embedded sections, hepatocytes (H) appear enlarged and foamy, admixed with clusters of foamy macrophages rimmed with pericellular fibrosis in blue (trichrome stain, 200x). D. Dense bridging bands of fibrosis (blue) appear throughout the section, consistent with cirrhosis. Foamy macrophages cluster around portal triads (trichrome stain, 20x).

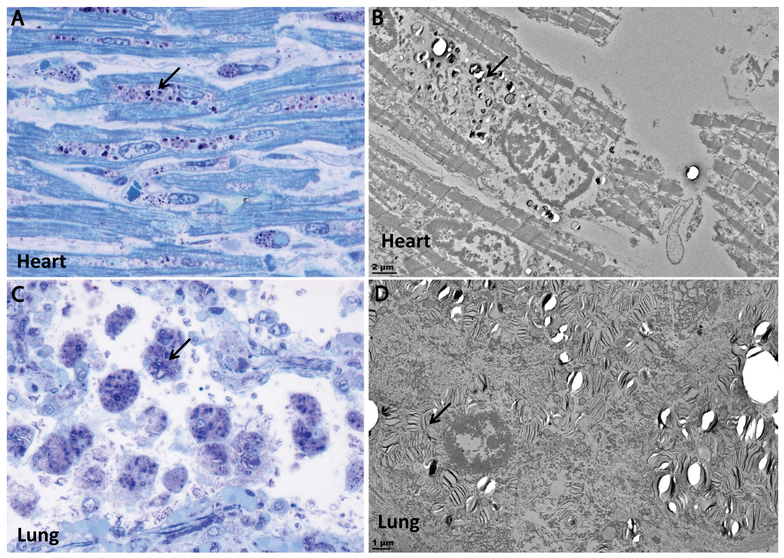

Figure 1: Sphingomyelin accumulation was present in the heart and lungs. A. In cardiomyocytes of the left ventricular free wall, sphingomyelin appears as purple globules in high resolution microscopy sections (1 micron epoxy resin section, modified toluidene blue stain, 1000x). B. Electron microscopy of cardiomyocytes demonstrates the "fingerprint" type whorls characteristic of sphingomyelin accumulation in Niemann–Pick disease (electron microscopy, scale bar = 2 microns). C. Alveolar macrophages of the lung are engorged with sphingomyelin, panel C. (high resolution light microscopy, 1 micron epoxy resin section, modified toluidene blue stain, 600x). Electron microscopy demonstrates the 'zebra body' and 'fingerprint' architecture of the accumulated sphingomyelin in alveolar macrophages, panel D (scale bar = 1 micron).

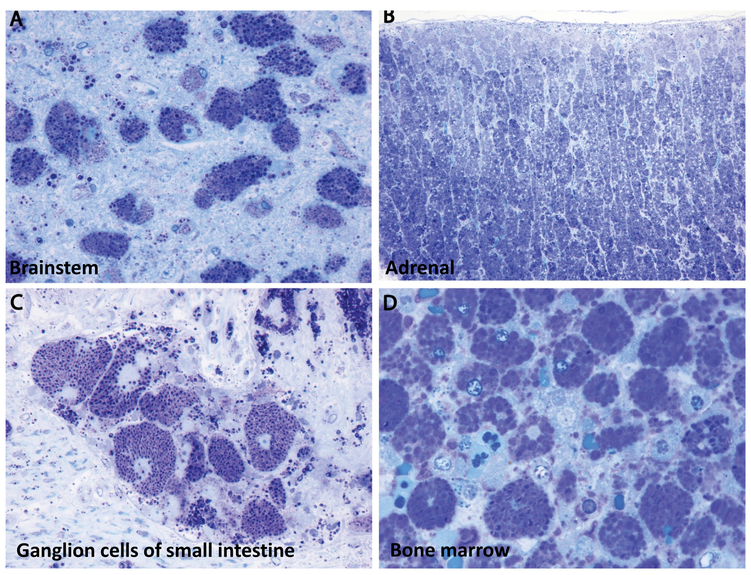

Figure 3

Figure 3: Additional affected cells and organs. A. Neurons of the brainstem. B. Cells of the adrenal cortex. C. Ganglion cells of the small intestine. D. The bone marrow is filled with typical "Niemann-Pick" cells. (high resolution light microscopy, 1 micron epoxy resin sections, modified toluidene blue stain, magnifications 600x, 100x, 600x, and 1000x, respectively).

Summary and Discussion

There are very few pathology reports about Infantile Neurovisceral ASMD (NPD A) in the literature[2]. Natural history reports[3] describe a pattern of disease progression, often beginning with detection of organomegaly. This is followed by neurologic, gastrointestinal, and respiratory symptoms, along with feeding difficulties, failure to thrive, irritability, and death at an average age of 27 months. The patient reported here followed a similar clinical course. Currently, there is no effective treatment for this form of the disease. The use of bone marrow transplant and stem cell transplant have been met with limited success[4]. The significant CNS pathology reported here in particular, highlights the challenge of developing a treatment capable of accessing and treating all disease compartments affected by this disorder.

This post mortem study provided a valuable opportunity to better appreciate the dramatic cell pathology of infantile neurovisceral ASMD. The reported complete deficiency of enzyme activity results in widespread sphingomyelin accumulation and multi-organ disease. It also serves as a reminder of the potential evolution of subclinical pathology evolving in other organs in patients with partially deficient enzyme activity.

Many of the lysosomal storage disorders present as a spectrum of disease severity. The level of residual enzyme activity is determined by the specific gene mutation, of which there are many. As a result, levels of residual enzyme activity vary from patient to patient, from near normal to absent. This variation, in turn, may correlate with the severity of pathology, clinical signs, and symptoms.

When we have the opportunity to closely examine the effects of a near-complete deficiency of enzyme, we see that virtually every cell has the potential of being affected and contributing to whole organ dysfunction. This should bring awareness to the clinician of potentially more subtle symptoms which could be overlooked in the partially deficient patient, due to a focus on more obvious signs (eg, hepatosplenomegaly), but that nevertheless may be a consequence of the disease and should be considered in the differential diagnosis of each patient.

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Acknowledgments

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Disclosures

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