CASE IMAGE

Under Your Microscope

A 7-month-old boy with failure to thrive

Pulkit Rastogi1 | Kirti Gupta1 | Renu Suthar2 | Anmol Bhatia3 | Arun Bansal2

1Department of Histopathology, Post Graduate Institute of Medical Education & Research, Chandigarh, India
2Department of Pediatrics, Post Graduate Institute of Medical Education & Research, Chandigarh, India
3Department of Radiology, Post Graduate Institute of Medical Education & Research, Chandigarh, India

Correspondence
Kirti Gupta, Department of Histopathology, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India
Email: kirtigupta10@yahoo.co.in

1 CASE DESCRIPTION

A 7-month-old boy was admitted in paediatric emergency for fever and respiratory distress following surgery for bilateral inguinal hernia. His clinical course was characterized by failure to thrive with delayed milestones. Echocardiography revealed dilated cardiomyopathy. Bilateral cherry-red spots were noted on fundus examination. He progressively developed encephalopathy with poor spontaneous activity and poor visual fixation. On day 10 of illness, he developed respiratory distress and died due to cardiogenic shock followed by cardiac arrest.

A complete autopsy (including abdominothoracic organs and brain) was performed after an informed consent. The brain weighed 833 g, with a normal gyral pattern. No exudates were noted on convexities or base of the brain (Figure 1). On microscopy, the cortex revealed complete loss of normal cortical lamination. Numerous ballooned-up, foamy neurons and glial cells were identified in all sampled areas of cerebral cortex, hippocampus, brainstem, and choroid plexus (Figure 2A). CD68 immunostain highlighted these foamy cells. Other neuronal tissues including cranial nerves nuclei and myenteric plexus ganglia also demonstrated ‘storage cells’. The material was weakly positive with periodic acid-Schiff (PAS), was diastase resistant, and positive with Oil-red-O and Luxol-fast blue (LFB) (Figure 2B–E). Electron microscopy revealed membranous cytoplasmic bodies, consisting of multi-layered concentric lamellae (Figure 2F). LFB-PAS stain revealed myelin pallor, however, significant demyelination was not a dominant feature. Axons were preserved on neurofilament protein stain. The ganglion cells within plexus revealed similar storage material (Figure 2G). Extra-neural tissues like bone marrow (Figure 2H), spleen, thymus, lymph nodes, Kupffer cells of liver, pancreatic acini, cardiac myocytes, renal podocytes, smooth muscle cells of arterioles, alveolar interstitium also depicted vacuolated cells replete with similar material within their cytoplasm. Lungs revealed extensive bronchopneumonia and pulmonary haemorrhages which was cause of death.

FIGURE 1 Coronal slice of brain shows normal gyral pattern and absence of exudates on convexities and base of brain. No softening, ventricular dilation or focal lesions were noted

BOX 1 Slide scan
Access the whole slide scan at http://image.upmc.edu:8080/Neuropathology/BPA/BPA-21-01-001/view.apml

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2 | DIAGNOSIS

GM1 gangliosidosis, type I.

Genetic analysis performed on genomic DNA extracted from blood revealed a novel homozygous mutation in exon 11 of GLB1 gene (c.1071_1073delinsGG; p.Phe357LeufsTer26).

3 | DISCUSSION

Lysosomal storage disorders (LSD) are a heterogeneous group of genetic diseases with overlapping phenotypes, making their diagnosis challenging. GM1 gangliosidosis is one of the rare subtypes of LSD with an autosomal recessive inheritance and neuro-somatic manifestations that can manifest as infantile (type I), juvenile (type II) or rarely adult forms affecting children or adults (type III) (1). The disease is lethal in the infantile and juvenile forms. Infantile form presents with hypotonia and developmental delay between birth and 6 months of life. Type II (late infantile or juvenile form) presents with lag in motor and cognitive development, between 7 months and 3 years. Type III adult or chronic variant has a late onset (3–30 years) with milder clinical manifestations that include progressive extrapyramidal signs due to local deposition of ganglioside in the caudate nucleus. The underlying cause of GM1 gangliosidosis is a genetic deficiency of the lysosomal acid β-galactosidase leading to accumulation of GM1 gangliosides and related glycoconjugates in the lysosomes resulting in lysosomal swelling, cellular damage, and organ dysfunction (2). The severity of each type is inversely related to the residual activity of the mutant enzyme. Historically, clinical manifestations and brain dysfunction have all been attributed to accumulation of ganglioside in different tissues and particularly in the central nervous system (CNS). However, the exact mechanisms underlying the disease pathogenesis are incompletely understood. Folkert and colleagues have proposed an indirect role of this metabolic defect in myelin development and delayed myelination as possible patho-mechanisms in autopsy cases of infantile GM1 gangliosidosis (1). Clinical features, such as coarse facial features, gingival hypertrophy, corneal clouding, cherry-red macula, skeletal dysplasia, hepatosplenomegaly, vacuolated lymphocytes, in addition to a history of psychomotor regression raises the clinical suspicion of GM1 gangliosidosis. Conventional clinical clues, histopathology, electron microscopy and enzymatic assays with fibroblast culture are time-tested techniques helpful in diagnosing these disorders.

The index case illustrates extensive deposition of storage material in almost every organ of the body including CNS, cranial nerves, peripheral nervous system and extracranial organs. The storage cells with vacuolated cytoplasm contained stored ganglioside positive with PAS-diastase resistant, Oil-red O, and LFB. Within CNS, stored ganglioside was seen within neurons, astrocytes, choroid plexus, neuronal processes with vacuolated myelin, and nuclei of the brain stem. The myenteric plexus constituting the peripheral nervous system was also replete with storage material with vacuolated appearance.

Morquio type B or mucopolysaccharidosis type IVB (MPS IVB) and GM1 gangliosidosis share the same enzyme defect (β-galactosidase) due to mutations in GLB1 gene (2, 3). Morquio type B while being less...
frequent than gangliosidosis is characterized by skeletal and connective tissue abnormalities, corneal clouding, cardiac involvement, and increased urinary excretion of keratan sulfate but lacks CNS involvement in comparison to GM1 gangliosidosis. Moreover, in Morquio type B, the mutant enzyme exhibits reduced catalytic activity and hydrolytic activity for keratin sulfate and oligosaccharides, but normal activity for ganglioside GM1. Ganglioside GM1 is mainly stored in neuronal tissue, while keratan sulfate mainly accumulates in cartilage, which explains the different phenotypes observed in Morquio type B and GM1 gangliosidosis that share the same enzyme defect. A total of 102 mutations have been reported in *GLB1* gene in GM1 gangliosidosis; however, there is extensive molecular heterogeneity hindering a clear genotype/phenotype correlation. Mutations in exon 2, 5, and 6 are most commonly reported (2).

Galactosialidosis is another storage disease characterized by deficiency of β-galactosidase in combination with neuraminidase (2). The clinical presentation of this disease partially overlaps with GM1 gangliosidosis; however, the predominant clinical manifestations of galactosialidosis are attributed to the severe neuraminidase deficiency rather than the partial deficiency of the β-galactosidase enzyme.

Currently, symptomatic and supportive therapy is available for patients. Bone marrow transplantation and gene therapy are promising approaches in such disorders, which are being actively explored in animal models (2).

In conclusions, this case highlights the lethal effects of extensive deposition of ganglioside in CNS and extracranial organs in a genetically proven case of GM1 gangliosidosis.

**KEYWORDS**

autopsy, GM1 gangliosidosis, neuropathological findings, Zebra bodies

**CONFLICTS OF INTEREST**

The authors have declared no conflicts of interest for this article.

**AUTHOR CONTRIBUTIONS**

Pulkit Rastogi: Data acquisition, critical review of literature, autopsy analysis and assisted in manuscript writing; Kirti Gupta: Data acquisition, critical review of literature, autopsy analysis and manuscript writing; Renu Suthar and Arun Bansal: Clinically managed the patient during life, and assisted in critical review of literature; Anmol Bhatia: Performed and interpreted the radiology of the patient during life and assisted in critical review of literature. All authors have read and approved the final version.

**DATA AVAILABILITY STATEMENT**

Data sharing not applicable – no new data generated, or the article describes entirely theoretical research.

**ORCID**

Kirti Gupta  [https://orcid.org/0000-0002-9999-3203](https://orcid.org/0000-0002-9999-3203)

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