Case Report

Atypical cytomorphology of Gaucher cells on splenic aspirate in a rare case of Gaucher's type 2 disease

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Abstract

Gaucher's disease (GD) is the most common lysosomal storage disorder, with autosomal recessive transmission. The disease is due to glucocerebrosidase enzyme deficiency, resulting in accumulation of glucocerebroside in all organs. Among the clinical forms, type 2 is the rarest and has the most dismal prognosis.[1] We present a case of an infant found at 6 months of age with neurological symptoms and subsequent evolution of massive splenomegaly. The child being diagnosed with type 2 GD with atypical gaucher cells(GC's) on splenic fine needle aspiration cytology (FNAC).

Keywords: Lysosomal storage disorder, type 2 Gaucher disease, Splenic FNAC.

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INTRODUCTION

Gaucher disease (GD) was first described by Philippe Gaucher in his doctoral thesis in 1882, when he hypothesized that infiltration of enlarged cells in a spleen represented a ''neoplasm''.[2] The biochemical basis for the disease was elucidated 83 years later (1965) by Roscoe Brady's group at the National Institutes of Health.[2] The molecular basis of the disease was elucidated in the late 1980s, when the glucocerebrosidase gene mutations were identified.[2] GD is an inherited lysosomal storage disorder.[1]Its overall incidence is approximately 1:40,000 individuals.[3] It characterized by glucocerebroside (glucosylceramide) deposition in cells of the macrophage-monocyte system due to decreased activity of the enzyme beta-glucocerebrosidase (lysosomal enzyme that hydrolyzes glucosylceramide).[1] This enzyme is encoded by a gene on chromosome-1.[3] The disease is transmitted autosomal recessively and is due to a mutation of GBA1 gene encoding the enzyme synthesis.[1] In patients with GD, over 200 different mutant alleles of the gene have been identified.[1] Glucosylceramide accumulate in the bone marrow, liver, spleen, lung and other organs contributing to pancytopenia, massive hepatosplenomegaly and at times, diffuse infiltrative pulmonary disease.[4] The neuronopathic forms of GD are characterized by severe neuronal damage, astrocytosis and microglial proliferation.[5] The results of experimental studies carried out on mice with neuronopathic form of GD suggest that once the critical threshold of glucosylceramide accumulation is reached in neurons, a cascade of reactions is triggered that activates microglia, which releases inflammatory cytokines that amplify the inflammatory response, contributing to neuronal death.[4] The characteristic GC's are macrophages lipid loaded with wrinkled paper appearance and displaced nuclei.[5] Depending on the presence or absence of neurologic involvement, three clinical phenotypes have been described:

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- Type 1: Non-neuronopathic form, most frequently encountered;
- Type 2: Acute neuronopathic form, with rapidly progressive neurologic and visceral involvement and death in the first 2 years of life;
- Type 3: Chronic neuronopathic form – the neurovisceral involvements are slowly progressive.[5]

All three subtypes are inherited as autosomal recessive traits.[3] Some patients are affected by severe neurovisceral manifestations in infancy or early childhood but survive beyond 2 years of life, death occurring at the age of 3-7 years; these patients are considered to have an intermediate phenotype between type 2 and 3 disease.[5] For patients with type 1 and3, enzyme replacement therapy prevents disease progression; for children with type 2 disease treatment is supportive.[6]

CASE REPORT

A 6 months old boy coming from a young, non-consanguineous couple, with no antenatal or perinatal medical history, was admitted with malaise, mental retardation, excessive crying, refusal to feed and failure to thrive. The child had thin built, weight and height below normal for his age, increased tone, significant psychomotor delay, convergent strabismus noted by his mother since the age of 3 months and feeding difficulties: swallowing impairment requiring nutrition by tube. Cerebral CT scan showed mild global cerebral atrophy without any change in density of the cranial contents. During hospitalization, hypertonicity, myoclonic episodes in the upper limbs, enlargement of the spleen (massive splenomegaly) and liver (moderate hepatomegaly) confirmed by ultrasound, increased swallowing difficulties, despite symptomatic treatment and improved nutritious diet for age. Routine investigations suggested a mild microcytic hypochromic anemia, normal liver and renal function tests. The differential diagnosis suspected were cerebral palsy, global cerebral atrophy, anemia and storage disorder. So, bone marrow aspirations were done which were diluted even on repeated attempts. To reach the diagnosis US-guided splenic fine needle aspiration was done and smears were stained with Papanicolau (Figure 1), Hematoxylin and eosin(Figure 3) and leishman(Figure 2) which revealed singly scattered large round to oval cells with abundant cytoplasm and eccentric nucleus. Cytoplasm showed wrinkled paper appearance. At places few GC's showed atypical features(Figure 1 and 3) like multinucleation, central nuclei and hemophagocytosis. The GC's showed abundant finely granular or fibrillary Periodic acid Schiff (PAS) – positive material in the cytoplasm and eccentric nuclei (figure 4).

Table 1: Clinical Classification of Gaucher's Disease

Clinical Classification of Gaucher Disease			
	Type 1: Non-neuronopathic (Adult)	**Type 2: Acute Neuronopathic (Infantile)**	**Type 3: Chronic/Subacute Neuronopathic (Juvenile)**
Whom it strikes	Young adults/adults; most common in Ashkenazi Jewish population (1 in 450) 1 in 100000 general population	Infants rarely, with no ethnicity 1 in 100000 live births	Children/young adults, with no ethnicity; 1 in 50000 live births Norrbottnian variant: Sweden; until early adulthood
Distinguishing symptom	Distinguishing symptom Liver, spleen, and bone; no nervous system problems	Early nervous system problems, brainstem abnormalities	Later onset of nervous system problems: incoordination, mental deterioration, myoclonic seizures
Effects of disease	Varies from mild to severe	Death in infancy (age < 2 y)	Slowly progressive; becomes severe later in childhood
Glucocerebrosidase activity	Some activity, but much less than normal	Very little activity	little activity

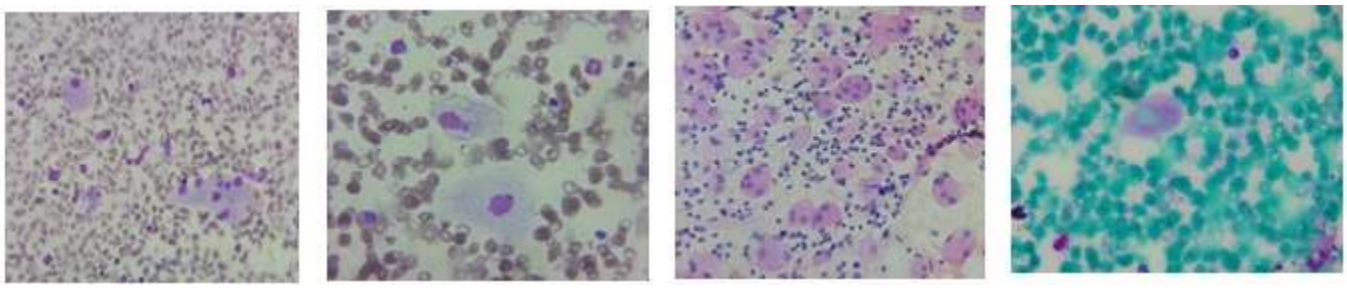

Figure 1: (400X PAP stain) Shows singly scattered Gaucher cells with cytoplasm showing wrinkled paper appearance and eccentric nucleus.
Figure 2: (1000X Leishman stain) – shows Gaucher cell.
Figure 3: (400X HandE stain) – Shows atypical Gaucher cells with central nucleus and multinucleation.
Figure 4: (400X PAS stain) – Shows finely granular or fibrillary PAS positive material in the cytoplasm and eccentric nuclei.

DISCUSSION

Historically, diagnosis of GD was usually based on morphological examination of the affected organ (e.g., bone marrow, spleen, liver).[7]Until 1966, when pseudo-Gaucher cells were described for the first time in chronic myeloid leukemia, it was believed that the presence of GCs in bone marrow was pathognomonic of GD.[7] Type 2 GD begins in the first 3-6 months of life, leading to progressive neuronal degeneration and death in the first 2 years of life; the incidence of this form of the disease is rare, estimated at 1/1,50,000.[8]

Two clinical subtypes have been described

- Acute neuronopathic form, with clinical onset after a symptoms free interval of 3-6 months of life and death before the age of 2 years;
- Neonatal-lethal form characterized by fetal hydrops, congenital ichthyosis, facial dysmorphism with perinatal or early mortality in uterus.[1]

The clinical manifestations of the classic form of Gaucher type 2 include hypertonia, seizures, strabismus, organomegaly, swallowing disorders, failure to thrive, stridor by laryngospasm, progressive psychomotor retardation; death can occur by aspiration or respiratory impairment.[1] The most frequent initial signs are hyperextension of the neck, swallowing disorders and strabismus, but there were cited cases of neonatal cholestasis as early onset of the disease.[1] Differential diagnosis is necessary with Niemann Pick disease.

Niemann-Pick disease is caused by a deficiency in sphingomyelinase, which leads to accumulation of sphingomyelin in the cytoplasm of macrophages.[2] The globules are small and relatively uniform in size, sometimes described as mulberry-like in appearance.[2] The cytoplasm in these macrophages is foamy and vacuolated as opposed to fibrillary in GC's.[2] In Tay-Sachs disease (hemoaminidase A deficiency), there is accumulation of GM2-gangliosidein the heart, liver, and spleen.[2] Involvement of the central nervous system with vacuolated neurons is predominant.[2] Pompe disease (acid maltase deficiency) is characterized by glycogen accumulation in hepatocytes and muscle cells, but the primary pathologic derangement is in skeletal and cardiac muscle.[2] Bone marrow aspiration or liver biopsy can identify GC's, but the enzyme assay is sensitive, specific, and much less invasive.[1] As we know pseudo-GC's may be found in the marrow of some patients with CML, type II congenital dyserythropoieticanaemia, thalassemia, Hodgkin lymphoma, multiple myeloma and AIDS.[3]Gaucher cells (GCs), the lipid-laden storage macrophages, are the pathologic hallmark of Gaucher disease (GD).[7] They are typically 20–100 μm in diameter with eccentrically placed nuclei and cytoplasm with characteristic crinkles and striations.[7]The GC's have abundant granular or fibrillary blue-gray cytoplasm with a wrinkled tissue paper–like appearance with abundant lightly periodic acid-Schiff–positive fibrillary material in the cytoplasm.[2] Only a few previous observations have indicated that sometimes GCs may display cytomorphology which is different from the classical description of GC.[7] These atypical GCs may be of a larger size or may contain a vacuolated, foamy cytoplasm, a centrally placed nucleus, more than one nucleus, cytoplasmic projections, hemosiderin and/or apparent phagocytosis of haematopoietic cells and/or thrombocytes.[7] A CD68 immunohistochemical stain usually highlights the GC's, as does an iron stain.[2] Treatment is supportive for this form of disease, because enzyme replacement therapy cannot reverse the neurological manifestations, due to recombinant enzyme's inability to cross the blood-brain barrier.[1] Thus, the current enzyme replacement therapy is limited to the treatment of non-neurological symptoms.[1] Substrate reduction therapy and pharmacological chaperone therapy are other ongoing research strategies for these patients.[1] For the families which include a member diagnosed with type 2 or 3 GD, it is mandatory to follow genetic counseling, which should contain direct enzymatic assay of beta-glucocerebrosidase and molecular testing of the GBA mutations on chorionic villous samples.[1] The case

we presented is a type 2 GD with onset in the first 6 months of life; the initial symptoms were psychomotor retardation, impaired swallowing and strabismus. Because we didn't find GC's in the bone marrow aspirate which were diluted, the diagnosis was delayed. Subsequently organomegaly, becoming gradually massive and failure to thrive, despite symptomatic treatment forced us to for splenic FNAC(USG-guided) which revealed classic GC's; along with few atypical GC's having (1) foamy cytoplasm (involving > 10% of the cytoplasm), (2) a centrally placed nucleus (the shortest distance between the nuclear membrane and the cytoplasmic membrane > 2/3 of the cell radius), (3) multi-nuclear GC's, and (4) apparent haemophagocytosis.[7] Multinucleated giant cells have been observed intermixed with typical GC's in an ultrastructural study by Takahashi and Naito.[7]

CONCLUSION

Neurological manifestations detected in the first months of life may be the first clinical sign of a type 2 Gaucher's disease (lysosomal storage disorder). The lack of Gaucher's cells in diluted bone marrow aspirate does not exclude the diagnosis of Gaucher's Disease; it should be considered in the differential diagnosis of children with unexplained hepatosplenomegaly.

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