CASE REPORT

Gaucher Disease: An Uncommon Cause of Pancytopenia in a 12-Year-Old Zambian Child - A Case Report

Uzima Chirwa[1, iD], Felix Sakala[2 iD], Sahar Mounir Nagib Butress[3], Natasha Mupeta Kaweme,[3,] Hamakwa Muluti Mantina[3], Manoj Mathew[1]

[1]*University Teaching Hospitals (UTHs)- Children's Hospital, Paediatric Haematology Unit, Private Bag RW 1X, Lusaka, Zambia.*
[2]*Mansa General Hospital (MGH), Department of Paediatrics and Child Health, Mansa, Zambia.*
[3]*University Teaching Hospital, Adult Hospital, Haematology Laboratory Unit, Private Bag RW IX, Lusaka, Zambia.*

ABSTRACT

Gaucher Disease (GD) is one of the rare genetic disorders resulting from glucocerebrosidase deficiency. GD is a rare cause of pancytopenia in children, presenting significant diagnostic challenges in settings with limited resources. The limited awareness of GD1 in developing countries, particularly among primary care physicians, often leads to delayed diagnoses and severe complications. The diagnosis is confirmed based on the identification of reduced glucocerebrosidase activity and genetic testing. This case report presents a teenage patient from Zambia with classical signs of type 1 Gaucher disease (GD1). She presented with transfusion- dependent anaemia, hepatosplenomegaly, pancytopenia and bone pain. The patient initially underwent splenectomy and later received enzyme replacement therapy due to non- availability initially, with clinical improvement. The case underscored critical diagnostic and treatment barriers in resource-limited settings. It also highlighted the urgent need for increased physician awareness and the development of a national rare diseases strategy to enable earlier intervention and improve patient outcomes.[1]

Corresponding Author:
Uzima Chirwa,
University Teaching Hospital (UTHs)-Children's Hospital,
P/Bag RW IX, Lusaka, Zambia. Email:
uzimachirwa@yahoo.co.uk

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Background and Literature Review

Gaucher Disease (GD) is a rare hereditary lysosomal storage disorder resulting from mutations in the glucocerebrosidase (GBA) gene on chromosome 1q21.31. This enzyme deficiency leads to the accumulation of glucocerebroside in various organs, causing a range of clinical manifestations, including pancytopenia, bone pain, hepatosplenomegaly, and in some cases, neurological symptoms.[2,3,4] The disease is categorized into three types:

- Type 1 (non-neuronopathic): the most common form, presenting from infancy to adulthood, particularly prevalent among Ashkenazi Jews. Presenting features include hepatosplenomegaly, bone pain, pathological fractures, and haematological

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complications such as easy bruising and anaemia.[2,5]

- Type 2 (acute infantile neuronopathic): Characterized by severe neurological involvement, with affected children often dying by age two.[6] Presents with hepatosplenomegaly, seizures, and strabismus. Neurological symptoms typically manifest within the first 6 months of life.[7] However, there have also been reports of cases where symptoms develop after 6 months and progress rapidly.[8]
- Type 3 (chronic neuronopathic): Features intermediate symptoms between Types 1 and 2, with a variable prognosis. It usually manifests in childhood, with life expectancy ranging from 10 to 15 years. Type 3 can be further subclassified based on neurological symptoms: type 3a is characterized by progressive myotonia and dementia, while type 3b is marked by isolated supranuclear gaze palsy.[9-11] Symptoms can overlap, and other forms of the disease, such as lethal perinatal or cardiovascular types, may not fit neatly into these classifications.[2,24]

GD has a global prevalence of 0.70 to 1.75 per 100,000 individuals.[12-14] Approximately 300 genotypes have been identified, correlating with the various phenotypical patterns of the disease.[15]

Diagnosis of GD involves clinical symptoms and signs, supported by tests such as full blood count (FBC) in which pancytopenia is a common finding, and imaging studies showing features like lytic lesions, osteopenia, and Erlenmeyer flask deformity. Elevated serum angiotensin-converting enzyme (ACE) levels due to the activation of splenic and hepatic macrophages are also common. Gaucher cells, which have a "crinkled paper" cytoplasm and are glycolipid-laden or foamy macrophages, can be observed in bone marrow aspirates.[16,17,23.] More specific and confirmatory tests include measuring glucocerebrosidase enzyme mean activity (less than 15% is diagnostic) and biomarkers like chitotriosidase, and glucosylsphingosine (**Lyso- Gb1**). Genotype testing for specific gene mutations is diagnostic.[24,25]

The mainstay of treatment is enzyme replacement therapy (ERT) with recombinant acid ß-glucosidase such as imiglucerase, for type 1 and some cases of type 3 Gaucher disease. This therapy significantly reduces the size of the spleen and liver and reverses other clinical manifestations. Unfortunately, ERT does not reverse the neuronopathic symptoms in types 2 and 3.[16, 23] Splenectomy may be beneficial for some children requiring multiple blood transfusions, with hypersplenism, or with splenic abscesses.[27, 28]

The purpose of this case report is to report the first confirmed Zambian GD case, advocate for improved diagnostics, and generate awareness of the disease.

Case presentation

A 12-year-old girl from Zambia's Central Province was referred to the University Teaching Hospital Children's Hospital with a one-year history of recurrent anaemia, abdominal distension, abdominal mass, backache, joint pain, easy fatiguability, fever, and weight loss. The abdominal mass was progressively enlarging. She had no bleeding tendencies. She received multiple blood transfusions to treat her severe anaemia, which led her to drop out of school. She continued to experience easy fatiguability despite receiving multiple blood transfusions at the local district hospital. Consequently, her mother sought treatment from traditional healer (Figure 1 displays the scarification marks resulting from traditional medicine), but the condition progressively worsened leading them to seek medical attention from a physician. She was HIV-negative and had no known contact with tuberculosis. She had no significant family history or consanguinity. Examination revealed conjunctival pallor, wasting (Body Mass Index 12 kg/m^2), abdominal distension, and severe hepatosplenomegaly (Figure 1). Examination of the respiratory, cardiovascular, musculoskeletal, and nervous systems was unremarkable. Our initial

working diagnosis was lymphoma. Routine laboratory tests were performed as shown in Table 1. The results indicated she had leukopenia, severe normocytic normochromic anaemia, thrombocytopenia, neutropenia, normal liver enzymes, normal albumin, and a markedly elevated angiotensin converting enzyme (ACE). Haemoglobin electrophoresis revealed the presence of haemoglobin A. Her X- ray results came back normal.

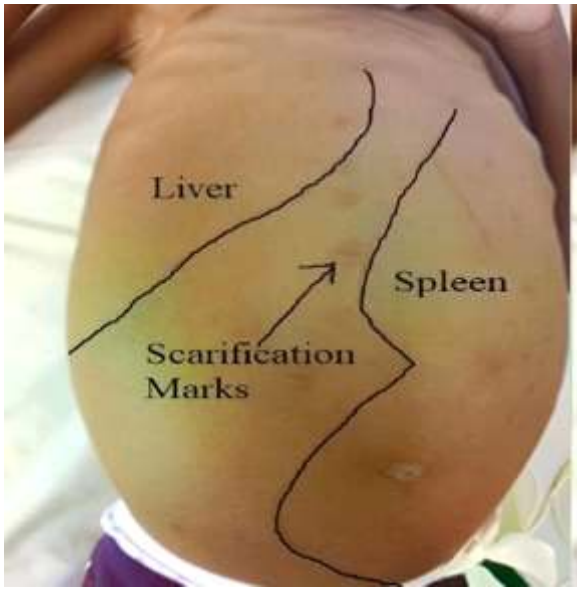


Figure 1: Shows Hepatosplenomegaly demarcated with black lines; arrow indicates scarification marks from prior traditional treatment

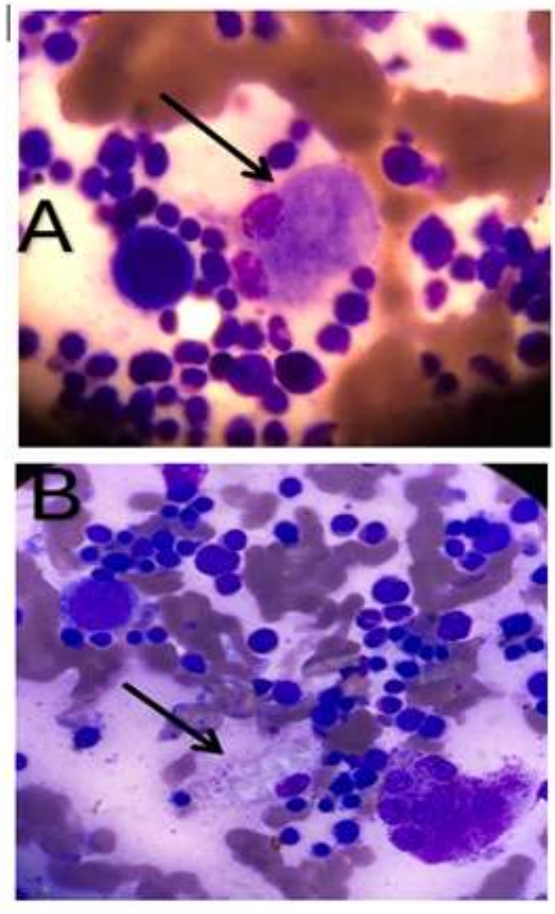
VARIABLE	REFERENCE RANGE	PATIENT
Leukocyte count	5.0- 13.0 x 10^9/L	**2.90 x 10^9/L**
Red blood cell count	4.0- 5.2 x 10^{12}/L	**2.92 x 10^{12}/L**
Haemoglobin	12.1- 16.3	**6.7 g/dL**
Mean corpuscular volume	79.1- 98.9	79 fL
Mean corpuscular haemoglobin	27.0- 32.0	29 pg
Platelets	150- 400 x 10^9/L	**65 x 10^9/L**
Neutrophil count	2.0- 7.0 x 10^9/L	**1.11 x 10^9/L**
Creatinine	23- 68	21 mmol/L
AST	5- 45	35.5 U/L
ALT	5- 45	32 U/L
Albumin	35- 50	38 g/L
Angiotensin converting enzyme (ACE)	8- 53	**432.81 U/L**

Other lab tests:

Echocardiography: Normal heart structure and function.

Computerized tomography (CT scan) of the abdomen results: Confirmed marked enlargement of the spleen, measuring 22.5 cm and liver measuring 17 cm. No enlarged abdominal lymph nodes.

Bone marrow aspirate: Hypercellular bone marrow, with megakaryopoietic and erythropoietic hyperplasia. Intermediate to large in size with eccentric nuclei and abundant light blue cytoplasm. Some cells display a foamy cytoplasmic appearance, most likely representing atypical Gaucher cells. Increased laden macrophages with iron debris were noted (Figure 2). The appearance suggests a lysosomal storage disease, most likely Gaucher disease.



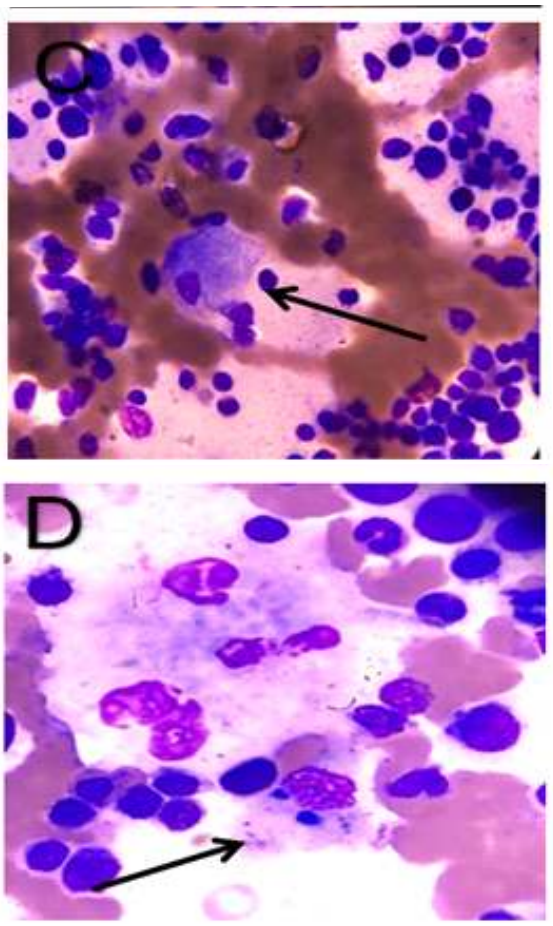


Figure 2: May Grunwald and Giemsa stain, morphological findings of the Bone Marrow Aspirate. (A, B and C) High power view showing a variable morphology of Gaucher cells, large cells with small eccentric nuclei, abundant foamy cytoplasm or wrinkled appearance. (×100 magnification). (D) Laden iron debris macrophage engulfs two normoblasts (100x).

Based on the bone marrow aspirate findings, further biochemical investigations (Table 2) and molecular genetic analyses (Table 3) were undertaken to confirm the diagnosis. Owing to the lack of local diagnostic capacity for these specialised tests, the samples were shipped to an accredited laboratory abroad. This reflects a significant limitation in the diagnostic work- up of rare diseases within Zambia, contributing to delays in definitive diagnosis and initiation of targeted therapy. Initial laboratory results classified her as a carrier because they couldn't find the second mutation due to technical limitations, but Greenwood Genetics later identified it, confirming the diagnosis of Gaucher disease.

Table 2: Biochemical investigations

VARIABLE	NORMAL RANGE	PATIENT
Beta Glucocerebrosidase activity	1.02- 77	**0.41 nmol/h/mL**
Chitotriosidase	7.0- 89.9	**1,714.31 nmol/h/mL**
Glucosylsphingosine (Lyso-Gb1)	3- 12	**1,317 nmol/L**

At presentation, the patient had severe anaemia, pancytopenia, and massive splenomegaly causing significant discomfort; features consistent with hypersplenism. Given the unavailability of ERT in Zambia at the time, and while awaiting the outcome of our application to an international ERT programme, we elected to perform a splenectomy. This interim intervention reduced transfusion requirements, relieved abdominal discomfort, and provided clinical stability while arrangements for ERT were underway.

A few months later, our application was successful, and we received Velaglucerase alfa (VPRIV) as a donation. Treatment was initiated at a dose of 1,600 units every two weeks, administered as a 60-minute intravenous infusion. Over 12 months of follow-up, the patient experienced marked clinical improvement: her haemoglobin normalised, liver span decreased to 11.5 cm, transfusion dependence ceased, and no adverse reactions occurred. Importantly, her quality of life improved substantially, allowing her to return to school and participate fully in play with her peers.

Table 3: Abnormal GBA sequencing analysis

Exon/Intron	Nucleotide change	Amino acid change	Zygosity	Type	Database
Exon 4	c.222_224del	p.Thr75del	Heterozygous	Likely pathogenic	HGMD CD00149
Exon 11	c.1448T>C	p.Leu483Pro	Heterozygous	Pathogenic	HGMD CM870010
Exon 11	c.1483G>C	p.Ala495Pro	Heterozygous	Pathogenic	HGMD CM900107
Exon 11	c.1497G>C	p.Val499=	Heterozygous	Pathogenic	DBSP rs1135675

DISCUSSION

Gaucher Disease, though rare, should be considered in cases of pancytopenia with accompanying symptoms like bone pain, and hepatosplenomegaly. The disease can masquerade as other haematological conditions, leading to delayed or missed diagnoses.[12] Many children, teenagers, and young adults in developing countries present with GD1 symptoms but remain undiagnosed due to limited physician awareness. Diagnostic delays can result in irreversible complications, as evidenced in our case. This is a common pitfall in modern medicine and can lead to errors in diagnosis and treatment. The clinical presentation of a patient should guide the diagnostic process, not solely the laboratory results, as was the case with our patient initially, which can sometimes be incorrect or misleading.

Pancytopenia in GD is often due to hypersplenism and bone marrow infiltration by Gaucher cells.[18] The deficiency or reduced activity of the enzyme glucocerebrosidase causes substrate accumulation in reticuloendothelial organs like the spleen, leading to splenomegaly. This splenomegaly, through various mechanisms, induces pancytopenia as was the case in our patient. One such mechanism is secondary hypersplenism, which involves immune-mediated processes and blood pooling. Increased expression of interleukin- 12 (IL-12) in hypersplenism inhibits haematopoiesis and activates natural killer (NK) cells, which destroy all cell lines, causing cytopenia. Autoimmunity also plays a role, where unprocessed antigens from the liver escape into circulation, triggering autoantibody production in the spleen. These autoantibodies then destroy blood cells resulting in pancytopenia.[19-21]

As a result, GD patients may present with bleeding tendencies due to thrombocytopenia, increased susceptibility to infections due to leukopenia, and symptoms such as easy fatiguability, palpitations, and malaise due to anaemia.[19]

ERT for type 1 GD is exceedingly effective in reversing the visceral and haematological manifestations of GD. Thus, prompt diagnosis and treatment with ERT are crucial. Challenges in diagnosis and treating GD are not unique to Zambia; similar obstacles are frequently encountered in many other African countries, primarily due to limited access to advanced diagnostic tools and specific therapeutic options. A retrospective 11- year study conducted at the Children's Hospital in Rabat, Morocco, which reviewed 11 patients with GD, underscored the widespread diagnostic challenges. The study revealed that, in many cases, enzyme assays were either unavailable or underutilized, and even when the diagnosis was made, ERT was often not initiated due to its high cost.[22]

In Zambia, our experience mirrored these challenges. The patient presented with transfusion- dependent anaemia and significant hepatosplenomegaly. However, a delay in obtaining the correct diagnosis led to a prolonged hospital stay, keeping the patient away from her family and resulting in an extended absence from school. Due to the unavailability of ERT locally and delays in accessing treatment abroad, she underwent an elective splenectomy as a temporary measure to manage her symptoms. A total splenectomy is generally favoured over a partial splenectomy because of the risk of the remaining splenic tissue will inevitably continue to accumulate Gaucher cells. Without ERT to clear substrate, splenic regrowth and return of hypersplenism is highly likely, often within months to a few years.[29] Several months after this procedure, we successfully obtained ERT through a compassionate access program facilitated by a donor organization. Treatment was initiated promptly upon receipt of the medication. Having strong international partnerships can bridge the treatment gap for rare diseases, enabling timely access to life- changing therapies that would otherwise remain out of reach.

Following the commencement of ERT, the patient exhibited no adverse effects and demonstrated a marked improvement in her clinical condition. Her haematological parameters normalized progressively, and there was a significant reduction in liver size (the liver span is now 11.5 cm on ultrasound), indicating a positive response to therapy. Moreover, she has become transfusion-independent and reported complete resolution of her chronic bone pain- one of the debilitating features of GD.

Importantly, to the best of our knowledge, this represents the first confirmed case of Gaucher Disease in Zambia diagnosed using molecular genetic testing. This case highlights both the barriers faced in resource- limited settings and the transformative impact that timely and appropriate therapy can have on patients with rare diseases such as GD. There is an urgent need to increase awareness of GD in Zambia and to implement a structured national diagnostic strategy aimed at facilitating early detection and timely initiation of therapy. Such measures have been shown in other settings to improve clinical outcomes, reduced irreversible organ damage, and optimize resource utlilization.[30] In resource- limited settings, the establishment of referral networks and integration into existing health programs may be critical steps towards improving patient care.

CONCLUSION

Healthcare providers should consider Gaucher disease in patients presenting with pancytopenia and other related symptoms. A concerted effort is required to educate healthcare providers in developing regions about type 1 Gaucher disease clinical presentation and diagnostic approach. Establishing a rare paediatric diseases institute in Zambia could facilitate better management and care for such conditions.

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Author Contribution

All authors made substantial contributions to this manuscript, including patient care, biopsy specimen processing, follow-up, and the

drafting, revision, and approval of the manuscript for publication.

Conflict of interest

The authors declare no conflict of interest.

Consent.

Written informed consent was obtained from the patient's mother for the publication of this case report, including photograps.

ORCID iD

Uzima Chirwa iD https://orcid.org/0000-0003-1872-6240

Felix Sakala iD https://orcid.org/0009-0004-3391-5319

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