Yemen Journal of Medicine 2024;3(3):242–246

Yemen Journal of Medicine

Journal homepage: https://yemenjmed.com

Case-Based Review

Gaucher disease and pulmonary hypertension in adult Libyan female: A case-based literature review

Nadya Omran[1], Amnna Rayani[2], Elmukhtar Habas[2]*

[1]*Tripoli University Hospital, Tripoli, Libya*
[2]*Hamad General Medicine Hamad Medical City, Doha, Qatar*

ARTICLE INFO

Article history:
Received 27-10-2024
Accepted 28-11-2024
Available online 13-12-2024

Keywords:
Gaucher disease
Pulmonary HTN
Immunoglobulin deficiency

ABSTRACT

Gaucher disease (GD) is a rare autosomal recessive disorder that results from a deficiency in -glucosidase (GBA) activity due to a GBA gene mutation. GBA hydrolyzes glucocerebrosides into glucose. Deficiency of this enzyme causes accumulation of glucocerebrosides in cells and tissues. Gaucher cell infiltration into the interstitial tissue can be asymptomatic or can cause mild signs and symptoms, such as wheezing and cough. Progressive disease involves Gaucher cells filling the alveolar spaces, causing dyspnea, frequent infections, pneumonia, and exercise intolerance. We report severe pulmonary hypertension in a 41-year Libyan female patient with type 1 GD who was diagnosed at 17 years of age, responding to enzyme replacement therapy.

1. Introduction

Gaucher disease (GD) is a rare disease; however, it is the most common lysosomal storage disease, resulting from deficient -glucocerebrosidase (GBA) activity, inherited in an autosomal-recessive manner. Over 300 mutations have been identified in the -glucocerebrosidase gene located on chromosome 1q21.[1]

Gaucher's disease (GD) is a rare hereditary disorder caused by mutations in the GBA1 gene, leading to a deficiency in glucocerebrosidase (GBA; E. C3.2.1.45). This autosomal recessive lysosomal storage disease affects approximately 1 in 50,000 to 1 in 100,000 individuals in the general population. It has a wide range of severities. Historically, GD has been classified based on the degree and type of neurological involvement. Type 1 GD (GD1) is non-neuronopathic, occurring at any age, with Ashkenazi Jewish individuals having a high carrier frequency of 1 in 16.[2] In contrast, acute neuronopathic GD (GD2) typically presents within the first year of life and is characterized by a rapid neurological decline. Chronic neuronopathic GD (GD3) often begins in early childhood and has a wide range of neurological and non-neurological symptoms, with slow horizontal saccadic eye movements being the most common.[3]

Although the condition known as GD has been identified for nearly 140 years, significant progress has been made in understanding its phenotypic range and capacity to treat patients. This new knowledge has impacted the diagnosis and treatment of GD-induced pulmonary hypertension (PHTN), regardless of age. This case report and literature review aimed to provide a comprehensive overview of pulmonary HTN in GD type I with diverse clinical presentations and evolving diagnostic and therapeutic options in the presented case context.

1.1. Phenotypes of Gaucher disease

Three phenotypes of GD have been described based on the clinical features and natural history of GD.[4] Type I (GD1) is the most common, and may develop at

*Corresponding author.
E-mail addresses: habas1962@gmail.com (A. Rayani), habas1962@gmail.com (E. Habas).

https://doi.org/10.18231/j.yjom.2024.025

childhood or adulthood ages. Most GD type I patients do not have any neurological symptoms. Type II (GD2) and III (GD3) are less common and develop between infancy and adolescence, characterized by neurological damage. Type II is associated with the greatest morbidity and mortality and There is no effective treatment for this form of the disease. The main clinical features of adult Gaucher's disease are organ enlargement (liver and spleen), bone marrow infiltration leading to anemia, thrombocytopenia, leukopenia, skeletal involvement, bone pain and pathological fractures. GD is also associated with Parkinson's disease, cancer, lymphoproliferative disease, pulmonary hypertension, and gallstones.[5]

2. Pulmonary Hypertension in Gaucher Disease type 1

Pulmonary involvement is a rare life-threatening disorder, and pulmonary hypertension (PHTN) is the most serious pulmonary complication of GD1. PHTN was classified into five groups, according to the World Health Organization.[6] The classification is summarized in (Table 1).

Table 1: Classification of pulmonary hypertension (PHTN)

Group 1	Pulmonary Arterial Hypertension
Group 2	PHTN due to left-sided heart disease
Group 3	PHTN due to hypoxic and lung disease
Group 4	PHTN due to recurrent pulmonary thromboembolism
Group 5	PHTN due to chronic diseases such as sarcoidosis, hematological disorders, Gaucher, etc.

PHTN is a rare complication of Gaucher's disease type 1 (GD1).[7] The presence of PHTN in GD1 is associated with several other diseases and causes that lead to increased morbidity and mortality rates.[7] In GD, it has been reported that pathological lesions of both PHTN (plexogenic arteriopathy) and shunting (vascular dilatations in the lungs) can occur concurrently in the same patient. This has suggested a common pathophysiologic mechanism precipitating the end of the spectrum of pulmonary vascular disease.[8]

Three specific patterns of lung involvement have been identified in GD: (1) alveolar consolidation, which is caused by Gaucher cells filling the alveolar spaces and is typically observed in types 2 and 3 GD; (2) interstitial infiltrates of Gaucher cells with associated fibrosis, which is also typical of type 3 GD; and (3) PHTN, which is prevalent in type 1 GD.[9] The prevalence of mild PHTN identified by Doppler echocardiography was relatively high,[10] which is usually improved with Enzyme replacement therapy (ERT).[8] Recently, it was noted that severe and potentially life-threatening PHTN affects approximately 1% of GD patients which is a much higher incidence than in the general population (one in one million).[7] Furthermore, ERT improves mortality, morbidity, mortality and life quality.[11,12]

Infiltration of Gaucher cells into the interstitial tissue of the lungs can be asymptomatic or can cause mild signs and symptoms such as wheezing and coughing. Progressive disease involves Gaucher cells filling the alveolar spaces, causing dyspnea, frequent infections, pneumonia, and exercise intolerance. ERT, usually administered once every two weeks is the primary treatment for Gaucher disease. This involves the administration of a synthetic version of the missing GBA enzyme. The enzyme is taken up by cells in the liver and spleen, where it breaks down ERT and has been shown to effectively accumulate glucocerebroside, reduce the size of the organ, reduce the symptoms of Gaucher disease, and improve the quality of life of patients. It can reduce swelling and pain in the abdomen and limbs, improve blood counts, and reduce bone pain and risk of fractures. ERT may also prevent or delay the onset of more serious complications such as pulmonary hypertension and neurological problems. Although ERT is generally safe and well tolerated, it has some potential side effects, such as allergic reactions, fever, chills, and fatigue. Some patients may also experience infusion reactions, including flushing, itching, and shortness of breath.[13]

3. Diagnosis of Gaucher Disease

Diagnosing GD in pediatric patients can be quite difficult due to the highly variable symptoms and overlap with other conditions, which is further complicated by the increasing number of asymptomatic children identified through genetic screenings. The treatment of GD can be costly, time-consuming, and invasive, making it challenging to decide when and how to begin treatment. However, a better understanding of the different disease presentations at various ages (Table 2) can lead to improved treatment and patient/parental counseling.

4. Gaucher Disease Other Manifestation

Patients diagnosed with GD1 are classified as immunocompromised because of undergoing splenectomy and experiencing reduced release of inflammatory cytokines in Gaucher macrophages.[14] Reports have documented instances of other illnesses, such as tuberculosis, in people who have had delays or have not received treatment.[15] Cardiac complications, such as restrictive cardiomyopathy and calcifications of the valves and aortic arch, have been seen mostly in individuals with Gaucher disease type 3, particularly during infancy. In most instances, cardiac involvement has a limiting effect. Several instances of diastolic dysfunction, left ventricular hypertrophy, and restrictive cardiomyopathy have been observed as a result of infiltrative injury to the myocardium.[16,17] Earlier case studies indicate that high-dose ERT may enhance cardiac symptoms of heart failure and low left

Table 2: Clinical presentations of Gaucher disease at different ages

Newborn	Failure to grow
	Congenital discoloration (ichthyosis)
	Organomegaly (hepatosplenomegaly)
	Brain stem dysfunction- dysphagia and apnea
	Hematological abnormalities (low hemoglobulin, decreased platelets count)
During the 1st year	Anemia/thrombocytopenia
	Failure to grow
	Saccadic gaze abnormalities
	Progressive brain stem dysfunction-
	Cardiac valvular stenosis
	Convulsions
Childhood	Organ enlargement
	Hematological abnormalities, as above, and bleeding events
	Skeletal/bone involvement-avascular necrosis, osteopenia, pathologic fractures
	Bone pain crisis
	Epilepsy (usually myoclonic)
	Gaze abnormalities (saccadic type)
Adolescence	Organomegaly
	Delayed puberty
	Abnormal bleeding
	Bone pain crises of the skeleton and bone involvement

ventricular ejection fraction.[18] Endoscopic retrograde cholangiopancreatography is the primary treatment for gallstone disease in GD, effectively decreasing both the occurrence of complications and death related to the condition. Initiating ERT at an early stage not only saves the need for splenectomy but also greatly decreases the likelihood of developing pulmonary hypertension following spleen removal. Early pulmonary HTN development is a key risk factor for severe pulmonary HTN in individuals with GD1, and may be modified by early ERT initiation.

5. Mechanisms of Pulmonary Hypertension after Splenectomy

The link between GD1 and PHTN may be elucidated through several processes. Splenectomy is a significant factor contributing to PHTN in patients with GD1. Due to the common occurrence of hypersplenism and splenomegaly in systemic involvement, it is customary for most patients to undergo splenectomy early in the illness. Nevertheless, when the spleen is removed, Gaucher cells tend to develop in other tissues, particularly in the lungs. This accumulation may result in a condition called hepatopulmonary syndrome, which is characterized by interstitial lung disease, pulmonary capillary blockage, or the formation of aberrant vascular shunts.[8]

Additional processes that might account for the connection between splenectomy and PHTN include impaired functioning of the pulmonary endothelium, the presence of intimal fibrosis, medial hypertrophy, plexiform lesions, and an increase in platelet count after splenectomy.[19] The risk factors for severe PHTN are mostly splenectomy and its effects.

6. Case Presentation

A 41-year-old Libyan woman was diagnosed with type 1 Gaucher disease when she was aged 17. She had a history of breathlessness, palpitations, and headaches. Past medical history was not remarkable for any other illness, except for multiple blood transfusion sessions. The family history revealed that the two sisters and father had been diagnosed with GD. On examination, she had clinical features of anemia and hepatosplenomegaly at the age of 16 years, which was excised in the same year of diagnosis because of pressure symptoms. The diagnosis was based on a bone marrow biopsy and an enzyme assay. She received ERT two years after the diagnosis, and she had regular follow-up until the age of 27 years, although the ERT was on and off, mainly because the drug was not regularly available. At the age of 38, dyspnea and bilateral lower limb edema with paroxysmal nocturnal dyspnea and orthopnea were severe, and she was diagnosed with PHTN (mean pulmonary arterial pressure, 137 mmHg) in 2021 at the age of 41 years. Sildenafil (a phosphodiesterase inhibitor) for PHTN and digoxin in her heart. Currently, she is on ERT medications for both PHTN (bosentan) and heart failure (bisoprolol, furosemide, and spironolactone). Bosentan is a dual-endothelin receptor antagonist. Bosentan is used to treat PHTN by blocking the action of endothelin molecules, which otherwise promotes vasoconstriction and hypertension of the pulmonary vasculature.

The patient's body weight was 85 KG. Her investigation showed that anemia and thrombocytopenia were otherwise stable. Her lung function test results showed a restrictive pattern, and the ECHO showed severe tricuspid regurgitation and a mean pulmonary artery pressure of 137 mmHg. (Figure 1) shows a computed tomography (CT) scan of the chest and lungs.

The patient showed significant improvements in hematological, cardiac, and liver function parameters. (Table 3) presents the improved parameters after ERT.

7. Discussion

GD1 is the most common type of GD, particularly in Ashkenazi Jews, and it can manifest at any time from childhood to adulthood. Most GD type I patients had no neurological symptoms. In contrast, GD2 and GD3 are less common, develop between infancy and adolescence, and are

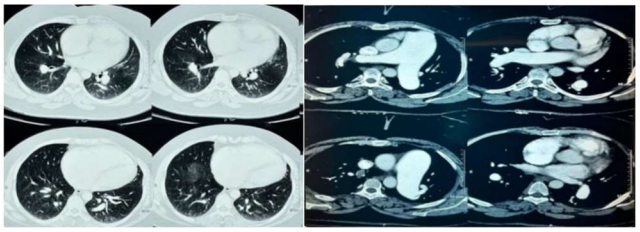

Figure 1: Patient CT findings consistent with the mosaic pattern lung related to pulmonary hypertension, consisting of regions of hypoattenuation due to hypoperfusion interposed with areas of hypo-attenuation where there is normal or excessive perfusion, dilated pulmonary arteries, and an enlarged right ventricle.

Table 3: Investigation results after 6 months of enzyme replacement therapy

Parameter	Pre/post-Enzyme replacement therapy
Hemoglobin	8.2/ 13.4
White blood cells	4/ 8.2
Mean corpuscle volume	86/ 90
Hematocrit	30.5/ 45
Platelets	64/ 112
Liver function test	NORMAL
Cardiac enzyme	Normal
PT and INR	Normal

characterized by neurological damage. Unfortunately, GD2 is associated with the greatest morbidity and mortality, and there is no effective treatment for this form of disease.

The main clinical features of adult Gaucher's disease are organ enlargement (liver and spleen), bone marrow infiltration leading to anemia, thrombocytopenia, and leukopenia, and skeletal involvement Leading to bone pain and pathological fractures. There is also an association with Parkinson's disease, cancer, lymphoproliferative disease PHTN, and gall bladder stones.[5]

PHTN risk factors include ERT-naïve, asplenic patients, ERT-refractory asplenic patients, female sex, glucocerebrosidase mutations, positive family history, and ACEI gene polymorphisms. Pulmonary involvement is a rare life-threatening disorder, and PHTN is the most serious pulmonary complication of GD1.[20] PHTN affects approximately one-third of people with untreated GD1 and approximately 7% of people on ERT, with Gaucher cells infiltrating interstitial lung tissue. Several mechanisms may explain the relationship between GD and PHTN. Splenectomy is a major cause of PH in GD1 patients. As stated earlier, there are possible mechanisms of PHTN in GD1 patients; however, the exact mechanism(s) have not yet been established. Therefore, further studies are required to investigate this complication.

Our patient underwent splenectomy at 17 years of age, and PHTN developed 24 years later. Although the development of PHTN in our case occurred within the expected period, early diagnosis and a multidisciplinary approach, including PHTN-specific treatment and ERT, could delay pulmonary complications and improve the prognosis of our patient. However, further studies are needed to better understand the underlying mechanisms and optimal management of PHTN in Gaucher disease patients.

8. Limitations

Gaucher disease is a rare autosomal disease; almost all published data are case reports. PHTN rarely occurs in patients with GD type 1. Hence, owing to the secrecy of the data, writing a comprehensive review and conducting further worldwide studies are unthinkable. Further studies are needed to cover Gaucher disease, PHTN, and pulmonary complications.

9. Conclusion

Gaucher disease type 1 may lead to the development of PHTN, heart failure, and organomegaly. Although splenectomy is helpful and indicated for Gaucher disease, it may also induce severe PHTN. Enzyme replacement and PHTN therapy benefit patients clinically and hemodynamically. Thus, clinicians should be mindful of the potential for PHTN and cardiac involvement in GD patients, particularly in those receiving late or inadequate therapy. Regular follow-up and multidisciplinary team are helpful in Gaucher disease patient monitoring, disease progression, and optimizing treatment plans. More research is required to discover effective medicines for Gaucher disease and PHTN, to enhance the quality of life for people afflicted by this uncommon condition.

10. Consent

The patient and parents provided a written consent to publish the case anonymously.

11. Source of Funding

None.

12. Conflicts of Interest

None.

References

1. Behl T, Kaur G, Fratila O, Buhas C, Judea-Pusta CT, Negrut N. Cross-talk among GBA mutations, glucocerebrosidase, and -synuclein in GBA-associated Parkinson's disease and their targeted therapeutic approaches: A comprehensive review. *Transl Neurodegener*. 2021;10(1):1–4.
2. Nalysnyk L, Rotella P, Simeone JC, Hamed A, Weinreb N. Gaucher disease epidemiology and natural history: a comprehensive review of the literature. *Hematology*. 2017;22(2):65–73.
3. Sidransky E, Tsuji S, Stubblefield BK, Currie J, Fitzgibbon EJ, Ginns EI, et al. Gaucher patients with oculomotor abnormalities do not have a unique genotype. *Clin Genet*. 1992;41(1):1–5.

4. Phetthong T, Aroon TT, Khongkraparn A, Noojarern S, Kuptanon C, Wichajarn K, et al. Gaucher disease: clinical phenotypes and refining GBA mutational spectrum in Thai patients. *Orphanet J Rare Dis*. 2021;16(1):519.
5. Stone WL, Basit H, Mukkamalla SKR, Master SR. Gaucher Disease. StatPearls Publishing; 2023. p. 34.
6. Simonneau G, Robbins IM, Beghetti M, Channick RN, Delcroix M. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2009;54(1):43–54.
7. Lo SM, Liu J, Chen F, Pastores GM, Knowles J, Boxer M, et al. Pulmonary vascular disease in Gaucher disease: clinical spectrum, determinants of phenotype and long-term outcomes of therapy. *J Inherit Metab Dis*. 2011;34(3):643–50.
8. Mistry PK, Sirrs S, Chan A, Pritzker MR, Duffy TP, Grace ME, et al. Pulmonary hypertension in type 1 Gaucher's disease: genetic and epigenetic determinants of phenotype and response to therapy. *Mol Genet Metab*. 2002;77(1-2):91–9.
9. Lee RE, Yousem SA. The Frequency and Type of Lung Involvement in Patients with Gauchers-Disease. *Modern Pathol*. 1988;63(6):368–76.
10. Elstein D, Klutstein MW, Lahad A, Abrahamov A, Halpern IH, Zimran A, et al. Echocardiographic assessment of pulmonary hypertension in Gaucher's disease. *Lancet*. 1998;351(9115):1544–50.
11. Katsigianni EI, Petrou P. A systematic review of economic evaluations of enzyme replacement therapy in Lysosomal storage diseases. *Cost Eff Resour Alloc*. 2022;20(1):51.
12. Hayes RP, Grinzaid KA, Duffey EB. The impact of Gaucher disease and its treatment on quality of life. *Qual Life Res*. 1998;7(6):521–55.
13. Lazea C, Bucerzan S, Al-Khzouz C, Zimmermann A, ŞC Vesa, Naşcu I, et al. Cardiac Manifestations in a Group of Romanian Patients with Gaucher Disease Type 1 (a Monocentric Study). *Diagnostics (Basel)*. 2021;11(6):989.
14. Yağmur B, Nalbantgil S, Kayıkçıoğlu M. Two Case Reports of Progressive Pulmonary Hypertension with Type-1 Gaucher Disease: Efficient PAH-Specific Therapy and 1-Year Follow-Up. *Anatol J Cardiol*. 2022;26(7):584–92.
15. Mistry PK, Liu J, Yang M, Nottoli T, Mcgrath J, Jain D, et al. Glucocerebrosidase gene-deficient mouse recapitulates Gaucher disease displaying cellular and molecular dysregulation beyond the macrophage. *Proc Natl Acad Sci*. 2010;107(45):19473–78.
16. Roghi A, Poggiali E, Cassinerio E, Pedrotti P, Giuditta M, Milazzo A. The role of cardiac magnetic resonance in assessing the cardiac involvement in Gaucher type 1 patients: morphological and functional evaluations. *J Cardiovasc Med (Hagerstown)*. 2017;18(4):244–52.
17. Kundu S, Dasgupta MK, Majumder B, Pradhan S. Restrictive cardiomyopathy: a rare presentation of Gaucher disease. *Ann Afr Med*. 2021;20(2):138–40.
18. Spada M, Chiappa E, Ponzone A. Cardiac response to enzyme-replacement therapy in Gaucher's disease. *N Engl J Med*. 1998;339(16):1165–6.
19. Palkar AV, Agrawal A, Verma S, Iftikhar A, Miller EJ, Talwar A, et al. Post splenectomy related pulmonary hypertension. *World J Respirol*. 2015;5(2):69–77.
20. Ohura T, Inoue CN, Abukawa D, Chiba AT, Tanaka T, Kakizawa H, et al. Progressive pulmonary hypertension: a fatal complication of type I glycogen storage disease. *J Inherit Metab Dis*. 1995;18(3):361–3.

Author's biography

Nadya Omran, Consultant

Amnna Rayani, Professor of Hematology https://orcid.org/0009-0005-5161-6555

Elmukhtar Habas, Senior Consultant https://orcid.org/0000-0002-7754-8993

Cite this article: Omran N, Rayani A, Habas E. Gaucher disease and pulmonary hypertension in adult Libyan female: A case-based literature review. *Yemen J Med* 2024;3(3):242-246.