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Challenges in Diagnosing and Managing Gaucher's Disease in India: a Case Report of a Child with Massive Splenomegaly

Priyanka Shokeen MD[1]; Monika Hooda DNB[1]; Brijesh Kumar DCH, MD, CMO(SAG)[1]; and Santosh Kumar Pandey DNB[1]

1-Department of Pediatrics, Indira Gandhi Hospital, Dwarka.

Corresponding author: Dr. Brijesh Kumar, CMO(SAG), Room No.3305, OPD Block, Department of Pediatrics, Indira Gandhi Hospital, Dwarka, New Delhi-110070.

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ABSTRACT: A 3.5-year-old girl presented to the Department of Pediatrics, Indira Gandhi Hospital, Dwarka, Delhi with massive splenomegaly after being misdiagnosed with various conditions at primary care facilities and tertiary care hospitals for six months. She was eventually diagnosed with Gaucher's disease based on bone marrow aspiration and low levels of glucocerebrosidase enzyme. The case highlights the challenges in diagnosing and managing rare genetic disorders like Gaucher's disease in India.

I. INTRODUCTION:

Gaucher's disease is an extremely rare genetic disorder that affects the body's ability to break down a fatty substance called glucocerebroside. The accumulation of this substance in different parts of the body leads to various symptoms and complications. The case report describes a 3.5-year-old girl who presented with massive splenomegaly. She was initially considered to have conditions like kala-azar, tropical splenomegaly, thalassemia, and portal hypertension. However, after further investigations, the differential diagnosis was narrowed down to lymphoreticular malignancy or metabolic storage disorder. The bone marrow aspiration suggested the diagnosis of Gaucher's disease, which was further confirmed with a very low level of glucocerebrosidase enzyme. The rarity of the condition and the cost-prohibitive treatment led to a referral to a specialized center for rare diseases. This case highlights the sensitization of Gaucher's disease as the cause of gross splenomegaly and the need for specialized care for such conditions.

II. CASE PRESENTATION:

A 3.5-year-old girl was brought to the Department of Pediatrics, Indira Gandhi Hospital, Dwarka by her parents with complaints of a progressive bulge and firm lumpy feeling on the left side for the last nine months. She did not report easy bruises, bleeding from any site, bone pains, persistent fever, swelling anywhere else, or progressive pallor. She did not receive a blood transfusion and was never hospitalized earlier.

She was born to Hindu parents out of non-consanguineous marriage in Nainital City, Uttarakhand. The Pedigree chart is shown in Figure 1. The perinatal course was uneventful. She has a 7-month-old younger brother who is normal. There was no history of unexplained and untimely deaths, multiple spontaneous abortions, or any previously diagnosed disease on either the paternal or maternal side.

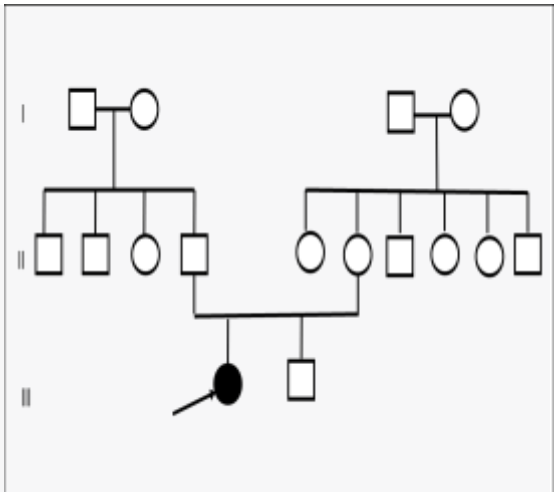

Figure 1 Family Pedigree

She had been seen by District Hospital at Nainital and after a few tests were asked to go to Delhi for further management. She was seen by pediatricians for a few months in Dwarka. She was found to have gross splenomegaly based on clinical examination and ultrasonography. Differential diagnoses included kala-azar, malariaand portal hypertension, but diagnosis remained elusive. She received some nutritional supplements and chloroquine during her visits to the health care professionals without any relief.

Examination showed an alert child with moderate pallor but, no edema/cyanosis/raised

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JVP/ lymphadenopathy/bone tenderness/ petechiae/ purpura. Her respiratory, cardiovascular, and neurological examinations were normal. Per abdomen examination showed a distended abdomen on the left side, no prominent veins, or pulsations; the liver was enlarged 5 cm, firm, and non-tender, and the spleen was enlarged 15 cm, firm. There was no evidence of ascitic fluid. Gross splenomegaly is depicted in Figure 2.

Figure 2

III. INVESTIGATIONS:

Complete blood count: Hemoglobin (Hb)-8.4 g/dL; Total leucocyte count-9100/mL; P39L54M06E01; Platelets- 1.1 lacs/mL; ReticulocyteCount- 1.7%.
Peripheral smear showed dimorphic anemia, few teardrop cells, mild anisopoikilocytosis and slightly reduced platelets. There were no haemoparasitesor other abnormal cells.

High-performance liquid chromatography: HbA-96.8%;HbA2- 2.2%; HbF- 0.5%.
Serum vitamin B-12 assay was normal.

Abdominal ultrasonography demonstratedgross splenomegaly with spleen size 16cm. Splenic and liver echotexture were normal. There was no ascites.Portal vein diameter andportal venous blood flow were normal. Chest Radiograph showeddiffuse bilateral interstitial opacities as shown in Figure 3.

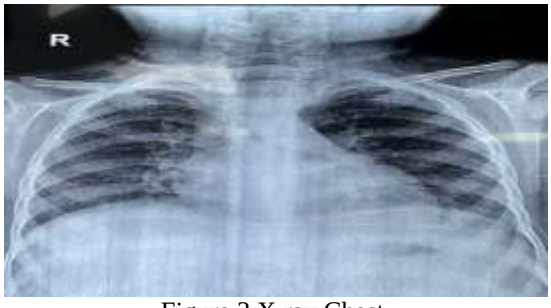

Figure 3 X ray Chest

Accordingly, the diagnosis was narrowed to lymphoreticular malignancy or metabolic storage disorder and it was decided to have bone marrow aspirate after consultation with the Department of Pathology. The results of bone marrow aspirate were Myeloid/Erythroid Ratio 1:1, mild erythroid hyperplasia with dyserythropoiesis,myeloid series in normal maturation; marked prominence of histiocytosis; many showing crumpled paper-like cytoplasm with eccentric nuclei suggesting Gaucher's cells. The findings of bone marrow aspirate are shown in Figure 4. It was advised to have blood glucocerebrosidase for confirmation of the suggested diagnosis.

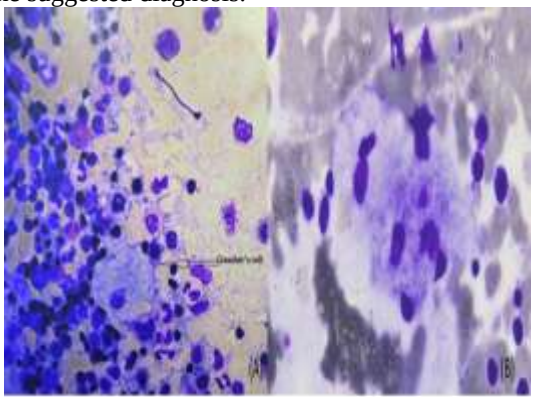

Figure 4 Bone Marrow Aspirate

Blood glucocerebrosidase levels were markedly reduced(1.2,normal:5-22). Based on the above clinical, radiological, and hematological findings, final diagnosis of Gaucher's disease(Type I) with lung involvement was made.

IV. DISCUSSION:

Common causes of gross splenomegaly in Indian context are:

- Lymphoproliferative disorders
- Thalassemia
- Leishmaniasis
- Tropical Splenomegaly Syndrome
- Portal Hypertension
- Metabolic Storage Disorders[1]

Leishmaniasis was indeed considered by one of the treating general pediatricianbut the serological tests were negative. Kala-azar(visceral leishmaniasis) is endemic in Bihar and there was negative travel history.Tropical splenomegaly syndrome was considered; however, she did not reside in the hyperendemic region and there was no persistent fever. Thalassemia and portal hypertension have been ruled out as high-performance liquid chromatography and Doppler studies for portal venous blood flow were normal.

This left possibilities of lymphoreticular malignancies and storage disorders. However, she did not have a family history giving any clues related to inherited diseases.

In cases where Gaucher's disease is a strong possibility, bone marrow aspirate is not necessary where enzyme level will be confirmatory.[2]As it has been pointed out bone marrow aspirate was highly suggestive of Gaucher's disease because of the presence of pathognomonic Gaucher's cells; the diagnosis was confirmed with very low levels of glucocerebrosidase enzyme levels.

However,the final diagnosis for this child who was being seen at several hospitals and pediatricians was no respite for this family with lower middle socioeconomic status. Now this was another challenge for further management of this child. It is indeed a challenge to provide appropriate and cost-effective treatment for rare diseases like Gaucher's disease in resource-limited countries like India. The high cost of enzyme replacement therapy is a major barrier to access for most families, and alternative treatment options like substrate reduction therapy are not easily available.

She was referred to the Center for Excellence for Rare Diseases at AIIMS, Delhi with prior communication. Several challenges can be ascertained for the management of Gaucher's disease in India. As this case represents, it was more than nine months before the correct diagnosis could be confirmed.

Gaucher's disease is an extremely rare disorder, and most pediatricians in India are not familiar with the signs and symptoms of the disease. This can lead to delays in diagnosis and treatment. Limited data are available on the prevalence of Gaucher's disease in India, making it further difficult to develop effective strategies for managing the disease. Incidence in world population varies from 1:40,000 to 1,50,000.[3] No reliable data exists in India. As it is inherited in an autosomal recessive manner, it is likely common in consanguineous marriages which are prevalent in Muslim and Southern India. However, there was no such family history in this child which further delayed the correct diagnosis.

Treatment has been available for the last few years in the form of enzyme replacement therapy.This allows the optimal quality of life and resolution of symptoms.[4,5] However, the one-time infusion cost comes to Rs.1.25 lakhs. Since the infusion is required for the whole life, the total cost may come in Crores. This is the ethical question in resource-limited countries like India where already Health services are overstretched. Health priorities like tuberculosis control, diarrheal diseases, and malnutrition which affect millions of children need to be balanced against diseases like Gaucher's disease.

Ministry of Health, Govt. of India has formulated a "National Policy of Rare Diseases" where these concerns seem to be addressed.[6]The National Policy for Rare Diseases in India aims to address some of these challenges by providing a framework for the management of rare diseases, including the creation of a registry for rare diseases, financial support for treatment, and the establishment of centers of excellence for rare diseases.However, the implementation of this policy is yet to be seen, and there are concerns about the feasibility and sustainability of providing long-term treatment for rare diseases.

V. CONCLUSIONS:

Above case of Gaucher's disease is a rare cause of gross splenomegaly which took about nine months for final diagnosis. This case of Gaucher's disease highlights the need for increased awareness and sensitization among general pediatricians about rare diseases like Gaucher's disease in India. There is also a need for a national register to track the prevalence of such diseases and provide support systems for affected families. At the same time, the high cost of treatment for rare diseases like Gaucher's disease also raises ethical concerns about allocating limited healthcare resources in resource-limited countries like India. Treatment at present is very expansive and beyond the reach of almost any Indian family. More research is needed to develop affordable treatment options for rare diseases which are relevant to India.

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Figure legends:

Figure 1: Pedigree chart showing the affected female child.

Figure 2: Figure showing gross splenomegaly in the child depicted by dashed lines.

Figure 3: Chest radiograph PA view showing interstitial infiltrates in both lung fields.

Figure 4: (A) and (B) show Gaucher's cell having crumpled paper-like cytoplasm with eccentric nuclei on bone marrow aspirate smear (100x, Giemsa stain).