ORIGINAL RESEARCH PAPER

Pathology

GAUCHER DISEASE- A RARE CASE REPORT FROM A TERTIARY CARE HOSPITAL IN NORTHERN INDIA

KEY WORDS: Gaucher, Rare, Splenomegaly

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ABSTRACT

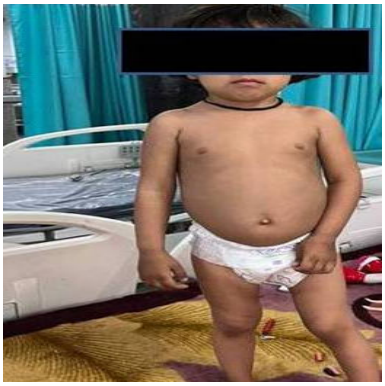
Gaucher disease is a rare lysosomal storage disorder with very few case reports from India. We intend to publish one such rare case with the aim of highlighting the detailed diagnostic approach to make an early and correct diagnosis of such a rare disorder. A three and a half year female presented to pediatric department with progressive abdominal distension since nine months. On examination, she was found to have massive splenomegaly . Investigations revealed bicytopenia. All relevant investigations were done step by step but the cause of splenomegaly was not evident . Bone marrow aspirate clinched the diagnosis as it showed presence of characteristic Gaucher Cells. Further confirmation of the diagnosis was done by biochemical level of glucocerebrosidase enzyme which was found to be extremely low. Molecular genetic analysis was also found to be positive, confirming the diagnosis.Also, genetic mutation detected, according to our case phenotype was rare. A step wise comprehensive approach to cases presenting with cytopenias and splenomegaly is required in order not to miss such rare cases of storage disorders.

INTRODUCTION

Gaucher disease, a rare autosomal recessive lysosomal storage disorder has a worldwide incidence of 1:40,000-1:85000. [1] There is a lack of studies giving exact incidence and prevalence of Gaucher disease in India, however, less than 1000 cases have been reported.[2] The incidence is higher in Jews (1: 450).[1] Gaucher occurs due to deficiency of the enzyme glucocerebrosidase because of a mutationin the acid-β-glucosidase gene. This leads to accumulation of glucocerebrosides in the lysosomes of macrophages. Gaucher cells are large (100 microns) with dark eccentric nucleus and prominent striations in cytoplasm. Electron microscopy reveals presence of elongated lysosomes loaded with lipids that are accumulated in double layer. [3] We report one rare case.

Case Report

A three and half year hindu female, presented with complaints of progressive abdominal distention [Fig 1], decreased physical activity and inability to gain height and weight from nine months. There was no history of similar complaints in the family.



"Fig1. Abdominal Distension in patient."

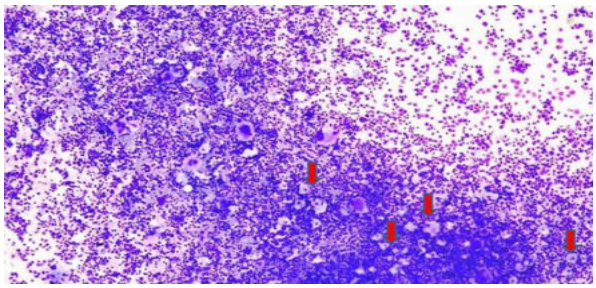
On general physical examination, pallor was present. Rest was within normal limits. On systemic examination, liver was palpable 5 cm below the right costal margin and spleen was 13-15 cm palpable below the left costal margin.. No signs of portal hypertension were noted. So, the patient on examination had pallor and hepatosplenomegaly.

Investigations were done as shown in Table 1.

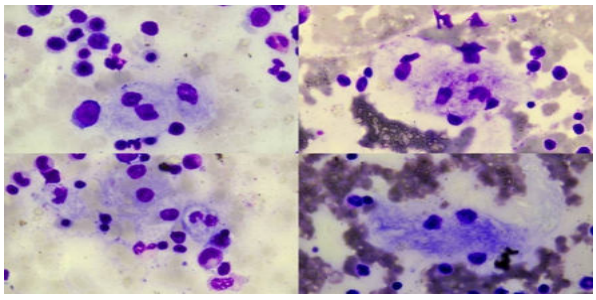
"Table 1- Relevant Investigations"

NAME OF INVESTIGATION	SIGNIFICANT FINDING
Complete Blood Count	Bicytopenia, Hb-8.4g/dl, Plt-1.1lac/mm3
Peripheral Smear	Microcytic hypochromic anemia, No signs of hemolysis, No Hemoparasite
Reticulocyte Count	Normal- 2%
Liver and Kidney Function Tests	Normal, Total Bil-1 mg/dl(0.1-1.2mg/dl),ALT- 40 IU/L(5-45IU/L), AST-30IU/L(5-45IU/L), ALP-201IU/L(93-309IU/L), Urea-14mg/dl(10-40mg/dl), Creatinine-0.4mg/dl(0.5-1.1mg/dl)
Folate, Vit B12, Hb HPLC	Normal, Folate- 15 ng/ml(5.2-20 ng/ml), Vit B12- 400 ng/ml(200-1100 ng/ml)
Kala Azar Strip Test	Negative
USG Abdomen	Massive Spleen, Mild Hepatomegaly
Colour Doppler of Spleno Portal Venous Axis	Normal, No Portal Hypertension
X Ray Chest	Diffuse bilateral interstitial infiltrate and scattered parenchymal opacities, suggestive of patchy pneumonitis

To summarise, the patient had bicytopenia with massive splenomegaly. Bone marrow aspiration smears were cellular with well spread marrow fragments. A marked prominence of histiocytes was noted, with crumpled paper like cytoplasm, eccentric nuclei raising the suspicion of Gaucher cells [Figure 2, 3].



"Fig 2. Bone marrow aspirate showing prominence of histiocytes, Giemsa, 100x."



"Fig 3. Characteristic Gaucher's cells with crumpled paper cytoplasm, Giemsa, 1000x."

In view of presence of clinical features i.e young child with inability to gain height and weight, having bicytopenia with massive splenomegaly, in conjuction with the above mentioned prominence of characterstic histiocytes, a possibility of Gaucher disease was suggested. To confirm, □-glucocerebrosidase enzyme levels in peripheral blood leucocytes were done and were found to be extremely low (1.2 nmol/hr/mg, normal range is 5.00-22.00 nmol/hr/mg). Targeted sequencing of GBA1 gene was done and revealed homozygosity for p.L483P.

DISCUSSION

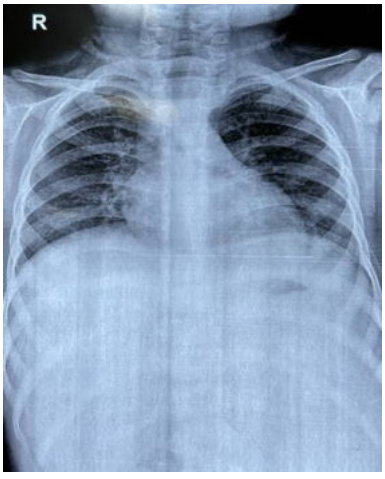
There are very few case reports from India, majority from southern or western India.[2,4] Few cases have been described in northern India. Our case is from Nainital, where it has not been reportedbefore. Very few Indian studies have partly described the burden of lysosomal disorders as summarised in Table 2.[5,6,7] None of these is from Northern India.

"Table 2- Summary Of Relevant Indian Studies describing prevalence incidence with demographic characteristics"

Sheth et al, 2013[5]	Prevalence of glycolipid storage disorders-48%, in their cohort, Incidence of Gauchers-16%, max cases from Maharashtra	Genetic analysis for Gauchers not done
Agarwal et al, 2015[6]	Prevalence of Gauchers in their cohort-32%, study from Mumbai-	Homozygous L444P - Most common, Homozygous G355D 9, Homozygous R359Q, Homozygous S356F ,Homozygous S125R,Homozygous F123 I/(c754A) ,Homozygous R448W , Rec Ex2 (c.44 T>C+ 46A>G+IVS2+ Ig> a: R170C (C.625 C>T, exon 6), L444P/A456P/R496 C/55 bpdel , L444P, R643C
Nalini and Cristopher [7]	High prevalence of GM2 gangliosidoses in Southern India	Genetic analysis not done

Gaucher has three clinical types 1) Chronic non neuropathic /Type 1 2) Acute neuropathic/Type II , worst prognosis .Neck and trunk rigidity, bulbar signs and oculomotor paralysis indicate CNS involvement 3) Subacute neuropathic / Type III both systemic and CNS involvement but the course is slower.[8] Our case belonged to type I as there were no symptoms or signs of CNS involvement.

The common presentations are hepatosplenomegaly, cytopenias, bone and lung disease. Hepatosplenomegaly (infiltrative) in turn leads to hypersplenism and thus cytopenias. Patients present with fatigue, bleeding and easy bruising as a result of both bone marrow infiltration as well as hypersplenism. Bone infiltration can present as bone pains ,pathological fractures as a result of marrow infiltration as well as cytokines produced by these cells.[9] Rare case reports presenting as lytic lesions in mandible have also been reported. [10] Bone disease can also present as bony crisis, mimicking presentation of hemolytic anemia which is the closest differential in a patient with splenomegaly. Commonly these patients present with failure to thrive and delayed milestones. Our case also had prominent vascular markings in both the lung fields alongwith scattered parenchymal opacities suggesting patchy pneumonitis [Figure 4]. This could also indicate underlying infiltration of lung by Gaucher cells.

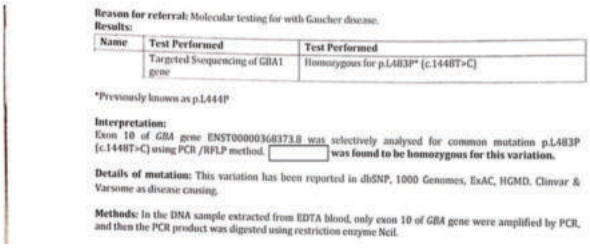


"Fig4. Chest X Ray showing patchy pneumonitis."

A wide array of differential diagnoses have to be considered in a young child presenting with bicytopenia with massive spleenomegaly. These include, infections, hemolytic anemia, hematologic malignancies and last but not the least storage disorders. Initially when the patient was admitted with a Hb of 8.4 gm% and a massive spleen, the first differential thought was hemolytic anemia. However, all signs for hemolysis were negative(jaundice, chronic leg ulcers , the peripheral smear , reticulocyte count, Hb HPLC). Though the patient was afebrile, malaria and kala azar were also ruled out as respective testing for both turned out to be negative. Next as the patient was unable to gain height and weight also, a hematologic malignancy was suspected , and a bone marrow aspiration was done. The bone marrow aspirate smears clinched the diagnosis, as they showed an increased number of Gaucher cells. The diagnosis was confirmed by enzyme levels. So, as described above , a systematic approachstarting

from detailed history and examination followed by investigations to rule out suspected causes should be done to arrive at a correct diagnosis.

The diagnosis suspected on a bone marrow aspirate is established by measuring the levels of glucocerebrosidase in blood leucocytes or in cultured fibroblasts. Detection of mutations is the upcoming modality of diagnosis. The most commonly reported is N370S substitution followed by L444P and 84GG in International Cancer Gene Consortium Registry.[11] However, pL444P, now known as pL483P is the most common in Indian patients.[12] Homozygosity for this mutation is associated with CNS involvement i.e. Type 2/3 disease.[13]Our patient was referred to AIIMS, Delhi where on mutation screening was found to be homozygous for the same. [Fig 5] Our case was also rare as was found to be homozygous for this mutation , but, there was no CNS involvement. This genotype phenotype mismatch is a known phenomenon in Gaucher disease which may be explained by effect of some modifier genes. Many genes have been studied as potential candidates having modifying effect like polymorphisms in CLN8.[14] Patients with milder symptoms were found to have higher levels of expression of the same in fibroblasts. Similarly it has been found that absence of SCARB2 mutations leads to mild Type 1 phenotype.[14] Increased TNF alpha expression due to homozygous rs1800629 polymorphism in its promoter region have been associated with non neuronopathic disease.[14]



Reason for referral: Molecular testing for with Gaucher disease.
Results:

Name	Test Performed	Test Performed
	Targeted Sequencing of GBA1 gene	Homozygous for p.L483P* (c.1448T>C)

*Previously known as p.L444P

Interpretation:
Exon 10 of *GBA* gene ENST00000368373.8 was selectively analysed for common mutation p.L483P (c.1448T>C) using PCR /RFLP method. [redacted] **was found to be homozygous for this variation.**

Details of mutation: This variation has been reported in dbSNP, 1000 Genomes, ExAC, HGMD, Clinvar & Varsome as disease causing.

Methods: In the DNA sample extracted from EDTA blood, only exon 10 of *GBA* gene were amplified by PCR, and then the PCR product was digested using restriction enzyme NciI.

"Fig 5. Targeted Gene Sequencing Report"

In resource poor countries the treatment is mainly palliative (transfusions, splenectomy, analgesics). Enzyme replacement therapy is now available and includes imiglucerase, velaglucerase alfa, and taliglucerase alfa.[3] However these are extremely expensive in Indian scenario. Oral substrate reduction therapy is another option available which acts by reducing production of glucocerebrosides by using inhibitor of glucosyl ceramide synthase.[3] Long term studies are needed to know complications and efficacy of these drugs.

CONCLUSION

Gaucher disease should be kept as a differential in children/ young adults presenting with cytopenias and massive spleen. Our case highlights the importance of a systematic comprehensive clinical, pathological and immunological approach to diagnose this rare disease.

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