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Short Communication

# Very rare condition of multiple Gaucheroma: A case report and review of the literature

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ABSTRACT

*Background:* This study presented a 3 years old boy with Gaucher disease (GD) who was treated with enzyme replacement therapy (ERT) for 19 months and then developed multiple Gaucheroma. Review of literature was performed simultaneously.

*Methods:* The medical chart and literature were reviewed. A boy presented at the age of 15 months with anemia, thrombocytopenia, and hepatosplenomegaly. GD was confirmed by enzyme assay and gene mutations. ERT was administered right after the diagnosis. When the boy was 3 years old, multiple masses were discovered during a regular checkup abdominal MRI and biopsy revealed Gaucheroma. We also reviewed 20 GD patients with Gaucheroma and Gaucher cell infiltrated lymphadenopathies.

*Conclusion:* Gaucheroma is a rare condition of regularly treated GD patients. This patient even showed poor response to doubled ERT doses. The imaging studies are necessary for Gaucher patients to detect Gaucheroma and determine their malignancy. Regular checkups are recommended in all GD patients even with regular treatment, due to the possibility of having deteriorating change, like Gaucheroma.

## 1. Introduction

Gaucher disease (GD) is the most common lysosomal storage disease (LSD) worldwide [1]. GD is an autosomal recessive disorder caused by mutation of the GBA gene [2,3]. The mutations cause decreased activity of β-glucocerebrosidase and result in the accumulation of glucosylceramide in macrophages [2]. This leads to the transformation of macrophages into Gaucher cells. It is believed that the infiltration of Gaucher cells into organs contributes to the presence of clinical symptoms.

A variety of mutations have been discovered in the GBA gene. Homozygous L483P(L444P) has been associated with a high risk of developing neurological impairment and a more severe clinical presentation of GD, whereas homozygous N370S often causes late-onset GD, and is the common mutation within the Ashkenazi Jewish community [2]. The primary GD phenotype can be classified into three types, non-neuropathic GD(type 1), acute and chronic neuropathic GD (type 2 and 3 GD, respectively).

The treatments for GD are intravenous enzyme replacement therapy (ERT), oral substrate reduction therapy (SRT) and pharmacological chaperone therapy. The principle of ERT is to produce a recombinant enzyme, which supplies the deficient β-glucocerebrosidase and breaks down the accumulated glucocerebroside [2]. The recommended dose is 60–120 IU/kg every other week. Anemia may be corrected during the first 6 months of treatment [4]. It should be noted that the platelet response varies depending on the degree of splenomegaly and the initial platelet count. In moderate cases, organomegaly will improve after

*Abbreviations:* GD, Gaucher disease; ERT, Enzyme replacement therapy; LSD, Lysosomal storage disease; SRT, substrate reduction therapy; DBS, dried blood test

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treatment for 12 to 24 months, however this also depends on the initial severity of organomegaly. The treatment response to skeletal pathology and pulmonary diseases are less significant [4].

Despite the current treatment options, patients with GD remain eligible to develop complications, including multiple myeloma and malignancies [2]. If a focal lesion develops in a patient with GD it should be carefully considered because of the increased risk of malignancy. However, Gaucheromas, which are pseudotumors formed by the accumulation of Gaucher cells have also been reported. The exact pathophysiology, clinical significance and possible prognosis associated with Gaucheromas remains unknown. This study presents the youngest patient, a 3 years old boy with GD who was treated with regular ERT from 15 months old. This patient developed multiple Gaucheroma after receiving ERT for 19 months. We also did the review of the all reported Gaucheroma patients.

## 2. Material and methods

The medical chart and literature were reviewed. A 15 months old boy was brought for a vaccination at his local hospital. The physical examination found he had hepatosplenomegaly. His mother reported that he had progressive abdominal distension for 2 months prior to his hospital visit. The boy's body height was below the 3rd percentile, and his body weight was within the 3rd to 15th percentile for his age. The developmental milestone showed he could not stand and still needed help to walk. He was born at full term and his past medical and family history were unremarkable. He had anemia (Hgb, 8.8 g/dL) and thrombocytopenia (Plt, 85,000/μL) at presentation. The boy was transferred to the tertiary center for further examination. A leukocyte enzyme assay reported decreased β-glucocerebrosidase activity (1.5 μM/L/h; reference, > 7.5 μM/L/h). Genetic study was performed and confirmed a homozygous mutation on the GBA gene at c.1448 T > C, p.L483P (L444P). A bone marrow aspiration was conducted, and the result revealed “wrinkled-paper cytoplasm” in his CD68+ histiocytes. The Bayley Scales of Infant Development showed a result compatible with his age, except for a mild delay in gross motor skills. The boy was diagnosed with GD at the age of 15 months.

Following his diagnosis, the patient received ERT (imiglucerase 60 IU/kg) every two weeks. Under regular following up, the patient was able to meet therapeutic goals for GD defined by Pastores et al.[5]. After 6 months of ERT treatment the patient's Hgb was increased to 11.6 g/L and his platelet count reached 118,000/mm$^3$. His dried blood test(DBS) CCL18 level had dropped to 136.25 ng/mL. The liver volume was 3.9 times higher than normal before ERT and had decreased to 2.3 times higher than normal after 19 months of ERT. The splenomegaly had also dropped from 24.3 times larger than normal to 8 times larger than normal. The repeated bone marrow exam revealed much less infiltration of Gaucher cells following the treatment.

Unfortunately, after ERT for 19 months, a regular abdominal MRI exam revealed a 3.5 × 2.3 cm hypointense under T1 lobulated mass, at S5 and S6 in the liver. (Fig. 1) Clustered enlarged lymph nodes at the mesenteric and inguinal regions were also discovered during the regular checkup. (Fig. 2).

A pediatric hematologist was consulted as hematological malignancy could not be ruled out. Therefore, the patient underwent an open biopsy and repeat bone marrow aspiration due to the suspicious malignancy conditions. Pathology of the liver mass and lymph nodes both revealed cell cytoplasm with “wrinkle-paper like” characteristics, which identified the Gaucheroma (Fig. 3A and B). Bone marrow studies were also confirmed as negative for immature cells and revealed a decreased number of Gaucher cells compared with the original exam at the time of diagnosis (Fig. 4A and B).

A remarkable decreased in the number of infiltrated Gaucher cells was noted after 19 months of ERT treatment. Because of the Gaucheroma, the patient started to receive double dose of ERT (imiglucerase 120 IU/kg) every two weeks. Unfortunately, the sizes of all the Gaucheromas didn't change after one year of ERT titration.

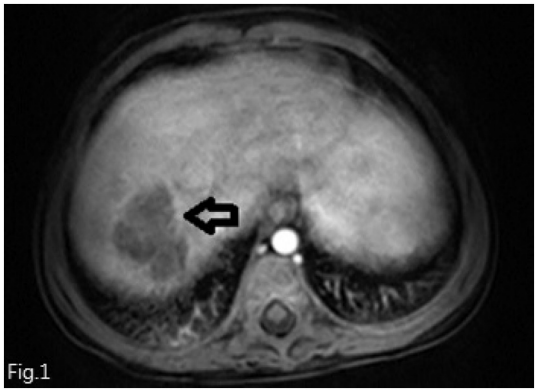


**Fig. 1.** T1 weighted MRI, noted a hypointense, with intersepted appearance, rim enhancement, and restricted diffusion mass (arrow), which measured 3.5 × 2.3 cm in size.

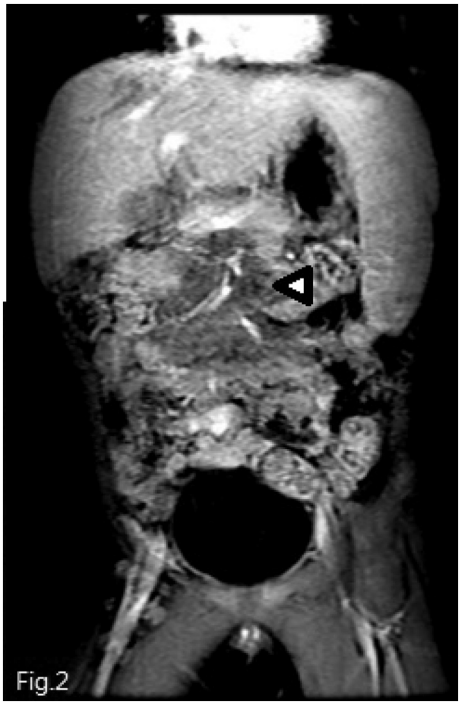


**Fig. 2.** Multiple clustered enlarged lymph nodes at mesentery (arrow head). Several small lymph nodes at bilateral inguinal regions.

We searched and reviewed the literature related to the Gaucheroma and Gaucher cell infiltrated lymphadenopathies. We found 20 reported patients(Table 1). The presence of Gaucheroma after the commencement of ERT ranges from 1.3 to 17 years. The patient in the current study developed Gaucheroma after 19 months of treatment, at 3-years old. This is thought to be the youngest patient to develop Gaucheroma. In patients who use a standard dose of 60 IU/kg every other week, Ivanova et al. reported that three patients developed extraosseous Gaucheroma [5]. There were two GD patients with a homozygous L483P(L444P) mutation. Another GD1 patient had a N370S/L444P. Poll et al. reported that a Gaucheroma presented in the liver, which mimicked focal nodular hyperplasia under MRI [6]. Korula et al. reported that a GD1 patient with homozygous c.1193G > A developed a liver Gaucheroma [7]. 14 patients developed Gaucher cell infiltrated lymphadenopathies in mesenteric, mediastinal, cervical or axillary were reported by 5 studies [8–12].

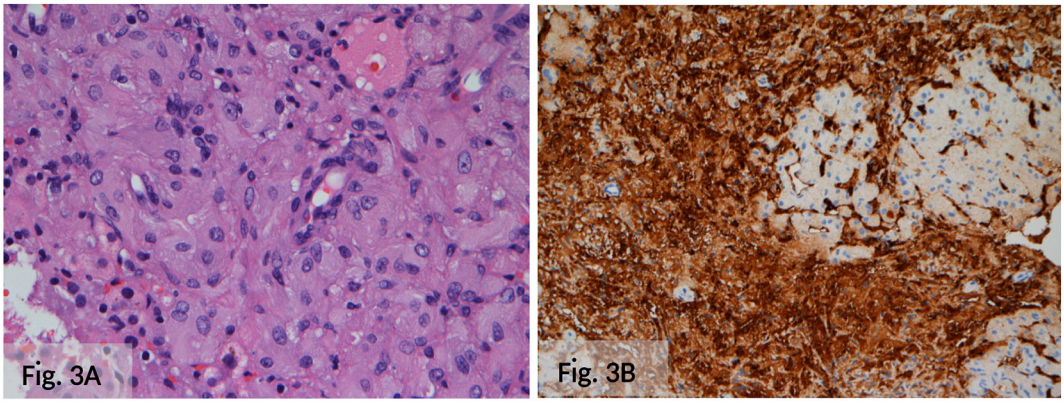


**Fig. 3.** (A) Biopsy of Gaucheroma under high-power field. The image shows the accumulation of glucocerebroside in Kupffer cells/macrophages, which formed Gauceher cells in the liver sinusoid and presented with a typical "wrinkle-paper like" appearance under the microscope. (B) The reactivity against CD163 showed a positive reaction.

## 3. Discussion

The present patient is the youngest reported as having Gaucheroma. Due to the involvement of multiple systems in GD, patients' treatment and care requires consultation between different specialists to achieve optimal outcomes [4,13].

Gaucheroma, a focal lesion, either multiple or solitary, composed of accumulated Gaucher cells has been well documented before the use of ERT [14,15]. The reported prevalence of splenic and hepatic lesions has ranged from 19 to 33% [16–18] and 6 to 20% respectively [18,19] for all ages. Since the commencement of ERT to treat Gaucher patients, the natural course of the disease has changed. A "pseudotumor" made up of a cluster of Gaucher cells (termed a Gaucheroma), is a rare condition which has been found in the liver, spleen, bone and lymph nodes [5–7] in patients who received ERT [6]. Its pathophysiology remains questionable and there is currently no treatment consensus. Kourla et al. proposed a combination of SRT or a higher dose of ERT as treatment for the Gaucheroma. However, the lesion mass showed interval reduction in size if a standard ERT dose was maintained [7]. In our study, there is no interval change of Gaucheroma after doubled the dose of ERT for one year. The responses of ERT vary in different organs and even in patients who share the same mutation [20]. In one autopsy studies in GD patients showed small clusters of Gaucher cells (about 10 cells each) in the liver after three years of ERT. The study reported another two patients, sharing the same genotype, similar ages at began of the ERT and similar treatment duration. The one who received higher doses of ERT (100 IU/kg/week) still showed more severe and extensive Gaucher cell infiltrations in organs at autopsy. These poor ERT responses point out the complexity of pathophysiology in GD and the influences of varies penetrations ability in organs, possible by the differentiate expression of the mannose receptors on the tissue macrophages which not only affect the uptake rate but also proper trafficking to the lysosome once the exogenous ERT is internalized in the cell [5,21,22].

The image presentation of Gaucheroma is very diverse and might be indistinguishable from malignancies, such as hepatocellular carcinoma or lymphoma [23]. In our study, we performed the biopsy of liver mass and reported the accumulation of glucocerebroside in Kupffer cells/macrophages and the positive reactivity against CD163 to prove this Gaucheroma lesion. Gaucheroma developed in the present patient despite him showing disease improvement. The condition also indicated the insufficiency of current treatment goals and biomarkers in evaluating GD patients.

GD is believed to alter the regulation of the immune system and inflammation, which may result in chronic inflammation. Gaucher cells share some features with the M2 phenotype, including CD163 and CD68, however, they do not express cytokines but they do express VEGF [5]. These findings are thought to be related to increased malignant risks in patients with GD and may contribute to the formation of Gaucheroma by attracts migration of these Gaucher cells [2,5,22]. Regenboog et al. proposed an algorithm for management the hepatic lesions in GD patients [23]. Due to the risk of malignancy in GD patients, the condition remains a great burden for physicians when deciding on treatment options. In Gaucher patients, regular imaging follow-up, including chest and abdominal MRI for possible interval changes may be required, even for the patients who have received regular ERT. The pathological proof was acquired in suspected patients

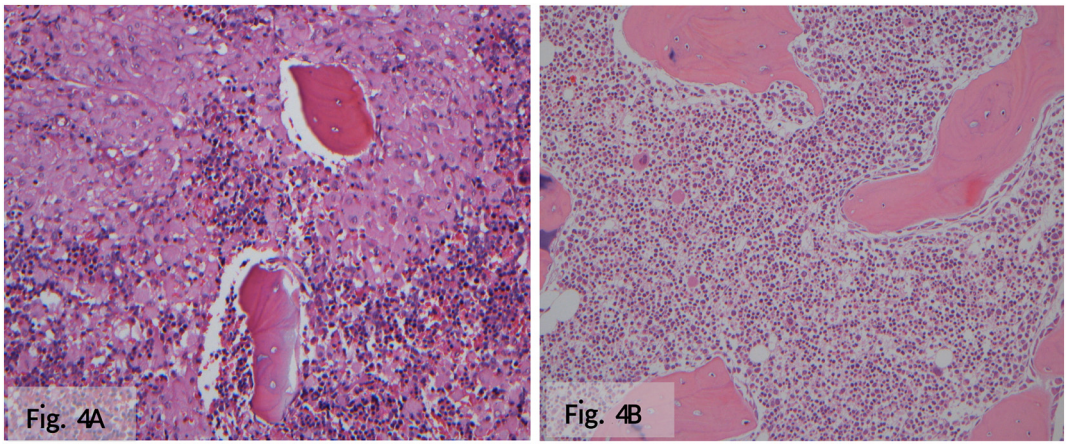


**Fig. 4.** Bone marrow biopsy under low-power field (A) before and (B) after the patient received ERT.

**Table 1**
List of the Reported Patients of Gaucheroma.
Adapted from Lee, B. H. et al. Progressive mesenteric lymphadenopathy with protein-losing enteropathy; a devastating complication in Gaucher disease. Mol Genet Metab 105, 522–524, (2012).

| Study | Type | Duration of treatment before Gaucheroma | Age of start treatment | Dose (IU/kg/QOW) | Genotype | Primary site |
|---|---|---|---|---|---|---|
| Tseng 2018[†] | 3 | 1.5y | 15mo | 60 | L444P/L444P | Liver Mesenteric LN |
| Lim 2002[8] | 3 | 2y | 13mo | - | - | Mesenteric LN |
| Fowler 2006[11] | - | 1.8y | 2.2y | - | - | Mesenteric LN |
| | - | 7y | 1y | - | L444P/L444P | Mesenteric LN |
| Burrow 2007[9] | 3 | 1.3y | 1.7y | 60 | D409H<br>L444P<br>A456P/A456P | Mesenteric and mediastinal LN |
| Poll 2009[6] | - | - | - | - | - | Liver |
| Yağci 2009[10] | 1/3[¶] | 3.4y | 18mo | 60 | L444P/? | Mesenteric LN |
| Lee 2012[12] | 3 | 3.6y | 1y | 40<br>120[§] | L444P/L444P | Mesenteric, cervical and mediastinal LN |
| Abdelwahab 2015[24] | 1 | 2y | 4y | 60<br>120[§]<br>< 60[*] | R359Q/R359Q | Mesenteric and mediastinal LN |
| | 1 | 2.5y | 1y | 60<br>< 60[*] | - | Mesenteric and mediastinal LN |
| | 1 | 3y | 4.5y | 60<br>< 60[*] | - | Mesenteric LN |
| | 3 | 3.5y | 18mo | 60<br>> 60[§]<br>< 60[*] | L444P/L444P | Mesenteric and mediastinal LN |
| | 3 | 1.5y | 2y | 60<br>< 60[*] | L444P/L444P | Cervical and axillary LN |
| | 3 | 7.5y | 1.5y | 60 | L444P/L444P | Mesenteric LN |
| | 3 | 3y | 2y | 60<br>30[*]<br>60 | L444P/L444P | Mesenteric and mediastinal LN |
| | 3 | 4y | 14mo | 120<br>< 60[*]<br>60 | L444P/L444P | Mesenteric, mediastinal, cervical, axillary LN |
| Korula 2016[7] | 1 | 3.5y | 15mo | 60 | Homozygous c.1193G > A | Liver |
| Ivanovae 2016[5] | 3 | 8.5y | 18mo | 60 | L444P/L444P | Osseous and Extraosseous |
| | 3 | 17y | 12mo | 60 | L444P/L444P | Extraosseous |
| | 1 | 5y | 65yr | 60 | N370S/L444P | Extraosseous |

LN: lymph nodes
[†] Our patient
[¶] Unable to differentiate phenotype due to young age
[§] Dose increased after diagnosed of Gaucheroma
[*] Dose decreased during Imiglucerase shortage

of malignancy. The exact mechanism of Gaucheroma was unknown. It might relate to different cell characteristics or differential expression of mannose receptors from other Gaucher cells. Further research was requested for improving the long-term outcome of Gaucher disease.

## 4. Conclusion

To the best of our knowledge, the current study presents the youngest reported patient of Gaucheroma, who have already received standing and regular ERT. Previous literature has reported that the onset of Gaucheroma ranges from 1.3 to 17 years after the commencement of ERT. All patients in the studies received the standard dose of 60 IU/kg every two weeks. The Gaucheroma failed to show improvement after titration the ERT doses. Regular imaging studies are recommended in GD patients, due to the possibility of having a deteriorating change, like Gaucheroma and the higher risk of malignancy in patients.

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## Competing Interests statement

The authors declare no conflicts of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Disclosure statement

The authors declare no conflicts of interest.

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