SYSTEMATIC REVIEW

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# Hepatic, Splenic, and Bone Marrow Gaucheromas: A Case Series and Systematic Literature Review

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## ABSTRACT

**Background & Aims**: Gaucher disease (GD) is one of the most common lysosomal storage diseases. It is characterized by the accumulation of glucocerebroside lipids in the macrophages, with liver, spleen and bone marrow frequently affected. The affected organs can develop tumor-like lesions (Gaucheromas), which are difficult to diagnose. We present the Gaucheromas and their ultrasonographic characteristics.
**Methods**: We selected Gaucheromas and their ultrasonographic characteristics found in the last 5 years during the periodical evaluation of 74 adult GD patients in Romania. All the patients had magnetic resonance imaging examination for comparison. A systematic review of all the Gaucheroma-related articles was performed to compare our results with the literature.
**Results**: Gaucheromas were found in 7 adult patients: 4 in the spleen, 2 in the liver and one affecting the bone. No malignancy ultrasound characteristics were found and neither on MRI exams. In the literature, 10 articles reported Gaucheromas, most of them in the liver and spleen in type 1 GD patients. All our patients were also type 1 GD, and the ultrasound aspect did not change during the 5 years follow-up.
**Conclusions**: Gaucheromas can be found in any patient with GD. Malignancies have to be considered unless proven otherwise. Imaging characterization (ultrasound and MRI) are useful as histopathologic examination is difficult to obtain in all cases.

**Key words:** Gaucher disease – Gaucheroma – ultrasound – splenic – hepatic – bone marrow.

**Abbreviations**: ERT: enzyme replacing therapies; GD: Gaucher disease; MRI: magnetic resonance imaging; SRT: substrate reducing therapies.

## INTRODUCTION

Gaucher disease (GD) is a rare inherited autosomal recessive disease. It is the most common lysosomal storage disease in the group of sphingolipidoses. These diseases are characterized by a dysfunction in degrading pathways of different metabolites with secondary accumulation in different organs. Gaucher disease was first described by Philippe Gaucher in 1882 when his work was focusing on spleen enlargement. His PhD thesis "De l'epithelioma primitif de la rate, hypertrophie idiopathique de la rate sans leucemie" first considered the enlargement of the spleen as non-malignant. Only in 1965 the specific pathways were understood and described by Brady et al [1].

With over 300 mutations of the glucocerebrosidase gene-GBA1, located on 1q21, the consequence is the accumulation of glucocerebroside lipids in the macrophages [2]. Symptoms are strongly associated with lipids accumulation in the organs. The most involved sites are the liver, spleen, bone marrow and nervous system. Although its large genotype that includes several variations, only three phenotypes have been described. The first is the most common, GD type 1- non neuropathic form, with low glucocerebrosidase activity, in which liver, spleen and bone marrow are mostly affected and the nervous system is rarely involved. The other 2 neuropathic forms are rarer: GD type 2 affecting the infants with very low enzymatic activity, high child mortality and severe neurological symptoms and GD type 3, similar to type 2 but with later onset (childhood or young adult) with better overall survival [3].

The diagnosis in modern laboratories is easily confirmed, as dried blood samples (DBS tests) are becoming widely available. The principal behind DBS testing is measuring enzymatic activity-beta glucocerebrosidase and glucosylsphinogosine (lyso-GL1) accumulation which can be computed, with gene mutations sequencing afterwards if needed. Also, treatment response can also be followed [4]. Although minimally invasive diagnosis methods are becoming widely available, more often, the diagnosis is confirmed following histopathological examinations of different organs. Splenectomy was widely used before specific therapy, as severe splenomegaly associated with secondary anemia and thrombocytopenia were difficult to manage, especially in young children. Bone fractures in pathological bone (severe osteopenia) are not rare, and bone biopsy are a must in these selected cases. Gaucher cells are to be found in blood samples, although non-specific, as pseudo Gaucher cells can be found in other storage diseases [5].

As the disease is caused by an enzymatic deficiency that will eventually lead to metabolites accumulation in different organs, treatment therapies are focused on these pathways: either by replacing the enzyme or reducing the substrate that the enzyme is supposed to degrade. Correcting misfolded enzymes through chaperones and gene therapies aimed to correct genotypes are novel directions. Enzyme replacing therapies (ERT) (intravenous administration), was the first approved treatment of GD. The rate of one dose/two weeks is considered to control the disease, with doses up to 60U/kg of body weight, but not less than 30U/kg body weight, as skeletal symptoms can worsen [6]. Substrate reducing therapies (SRT) (oral administration) is to be considered when intravenous administration is difficult (healthcare access, the patient's personal decision), unavailable or contraindicated, as long as the drug is not metabolized quickly through a specific cytochrome (CypD26 activity is to be determined first, with different dosage for specific types) [7].

Gaucheromas are very rare tumor-like lesions caused by localized accumulation of glucocerebrosides. They are non-malignant tumors, being hard to differentiate from malignancies in GD patients. As many retrospective studies found that malignant associations are not more common than in general population [8], a higher risk for developing multiple myeloma and lymphoma was reported in the current literature [9].

Ultrasonography is mandatory in all GD patients at least twice a year, as multiple other non-malignant diseases can occur (gall bladder stones- with a 5 times higher prevalence compared to the general population, up to 32% in GD type 1 patients [10]). Unusual abdominal examination findings should always be extensively investigated, as no malignant process can be excluded unless proven otherwise.

Pathogenic of GD will determine the localized accumulation of metabolites in the liver, spleen and bone marrow or lymph nodes, with specific symptoms.

We present our experience with the Gaucheromas and their ultrasonographic characteristics. As ultrasonographic findings are not specific, we conducted a systematic review of the literature and compared them with our findings.

## METHODS

We selected Gaucheromas and their ultrasonographic characteristics found in the last 5 years during the periodical evaluation of 74 adult GD patients in Romania. All the patients had a magnetic resonance imaging (MRI) examination for comparison. PubMed and Cochrane databases were searched for "Gaucheroma(s)". We found a total of 17 articles. After the exclusion of duplicates, partial results of later published articles, and reviews without imaging characterization, we were left with a total of 10 articles that were analyzed.

## RESULTS

Our data demonstrates the presence of Gaucheromas in 7 patients out of a total of 74 patients that were evaluated by ultrasound and MRI. We found Gaucheromas of the spleen in 4 patients, liver in 2 patients and bone in one patient. All our patients are GD type 1 patients, with ERT and stable lesions in the last 5 yearly examinations.

**Splenic Gaucheromas**

The spleen was the most frequent site for extraosseous Gaucheromas. The ultrasonographic and MRI findings were various, with single or multiple lesions. Focal hyperechoic lesions were found in 1 case and hypoechoic lesions in 3 cases. Doppler imaging was also used, with all the lesions showing low vascularity. Some cases had higher peripheral vascular Doppler signal. Mass effect (compression of surrounding tissues) was found in larger lesions. In 3 patients, multiple lesions were found, one of them with complete splenic architectural alteration. As lymphomas are more frequent in GD patients, we performed regular 6-month ultrasonography assessment, with further supplementary investigations if any abnormal dimensions or characteristics were found. No histology of the lesions was available in our patients, as all our described cases were stable imaging lesions, without any systemic signs of malignancies. The Gaucheroma diagnosis was most likely.

Our first case, a 68-year-old patient with type 1 GD with ERT for over the past 10 years, had a hyperechoic lesion with calcified perimeter in the spleen (Fig. 1a) and low Doppler signal. Magnetic resonance imaging showed the same characteristics, without any signs of malignancy (Fig. 1b).

In the second case, multiple Gaucheromas were detected, with a calcified and hypoechoic lesion in a 77-year-old female patient with type 1 GD, treated using ERT for over the past 10 years. Low Doppler signal and no mass effect were found (Fig. 2a).

The third case was a 46-year-old female patient with ERT presenting multiple hypoechoic splenic lesions, without mass effect (Fig, 3a) at ultrasound examination, and without MRI specific findings (besides slightly inhomogeneous aspect) (Fig. 3b).

The fourth case was a 53-year-old female with SRT, who presented multiple splenic Gaucheromas with architectural damage of the spleen. One of the lesions, found at the superior side of the spleen, had mass effect on the surroundings, peripheral vascularization (no specific intra-lesion Doppler signal) and inhomogeneous ultrasound appearance (Fig. 4a).

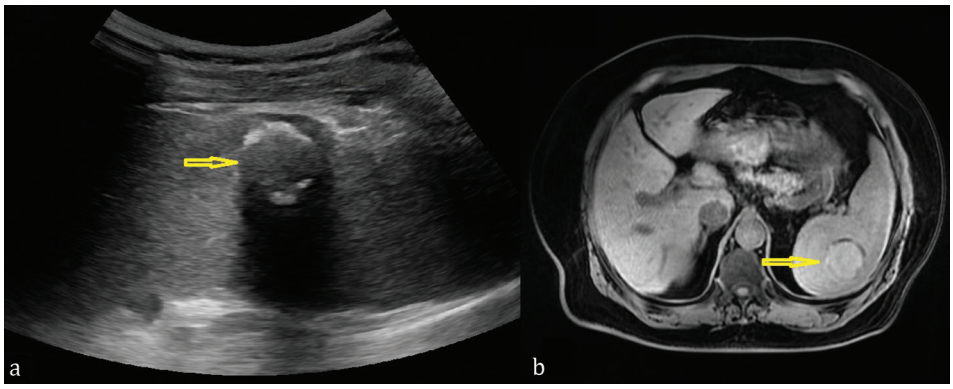


**Fig. 1**. Splenic Gaucheroma: a) ultrasound image; b) MRI appearance.

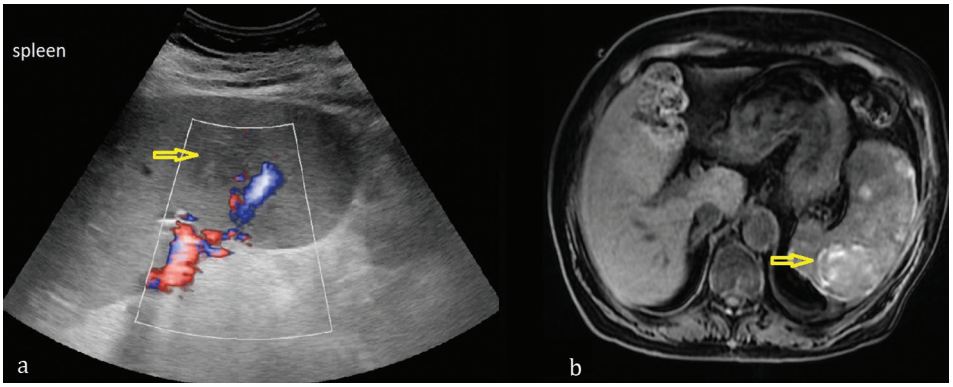


**Fig. 2**. Splenic Gaucheroma: a) ultrasound imaging: multiple hipoechoic lesions, without Doppler signal and mass effect; b) MRI imaging: multiple calcified focal lesions.

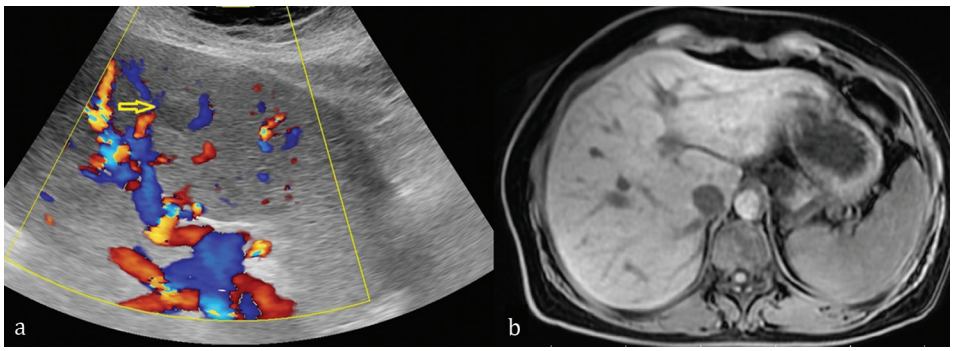


**Fig. 3**. Splenic Gaucheroma: hyperechoic lesion with calcified perimeter: a) ultrasound imaging: hypo echoic focal lesion without Doppler signal and without mass effect; b) MRI imaging: no specific findings (besides slightly inhomogeneous aspect).

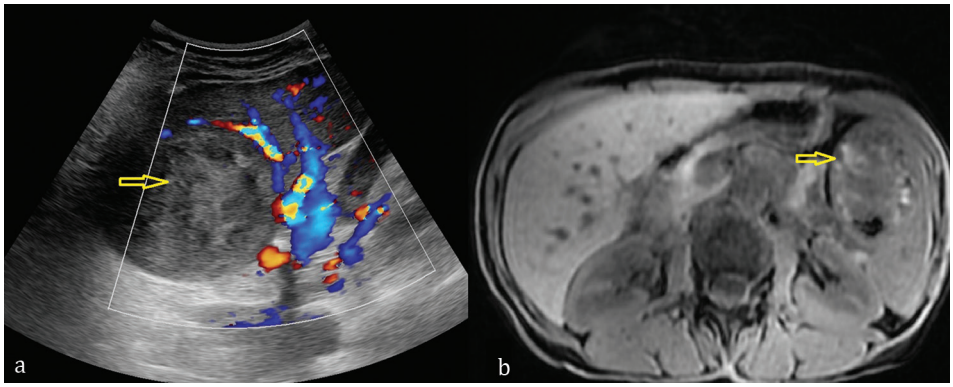


**Fig. 4.** Splenic Gaucheroma: a) ultrasound with Doppler signal: an inhomogeneous focal lesion with mass effect on the surroundings, peripheral vascularization (no specific intra-lesion Doppler signal). b) MRI of the spleen: architectural damage.

Besides the spleen's aspect, platelets and hemoglobin levels were in the normal range. No signs of malignancies were found.

**Hepatic Gaucheromas**

Hepatic lesions were the most difficult to differentiate from malignancy, as a wide range of differential diagnosis should have been considered. The ultrasonographic appearance was mostly hypoechoic.

A 53-year-old patient with inconstant ERT was found to have multiple hypoechoic lesions, without any mass effect on surrounding vessels (Fig. 5a). No other alterations were found to suggest malignancies (liver enzyme were in normal range, no signs of liver insufficiency and the tumor markers were in normal range). Magnetic resonance imaging showed no specific liver alterations. (Fig. 5b).

A 50-year-old female with ERT, presenting multiple hyperechoic lesions involving most of the liver. No mass effect on the surroundings and no specific vascularization were found (Fig. 6a). Magnetic resonance imaging examination found no specific aspect (Fig. 6b), with stable aspect for the last 5 years under high dose of ERT.

**Bone Marrow Gaucheromas**

We found a bone Gaucheroma on a pathological fracture and pseudarthrosis of the lower limb – tibia in a young 28-year-old patient without any other GD manifestations. No vascularization was found with no malignancy aspect (infiltration of the surrounding, periosteal damage) (Fig. 7).

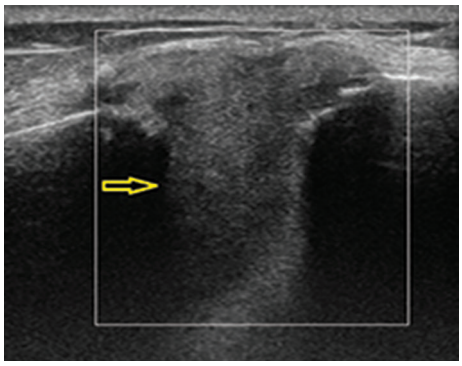

**Fig. 7.** Ultrasound of a bone lesion (Gaucheroma) without Doppler signal.

**Systematic Review**

Literature search results are summarized and presented in Table I [11-20]. Besides single cases that were reported, only 4 articles included more patients that were monitored and only 3 articles reported more than one Gaucheroma.

## DISCUSSION

**Splenic Gaucheromas**

Similar ultrasound and MRI findings of splenic Gaucheromas were described by Regenboog et al. [17], without correlation between ultrasound findings and MRI. The final diagnosis remains by histopathologic examination, but with a

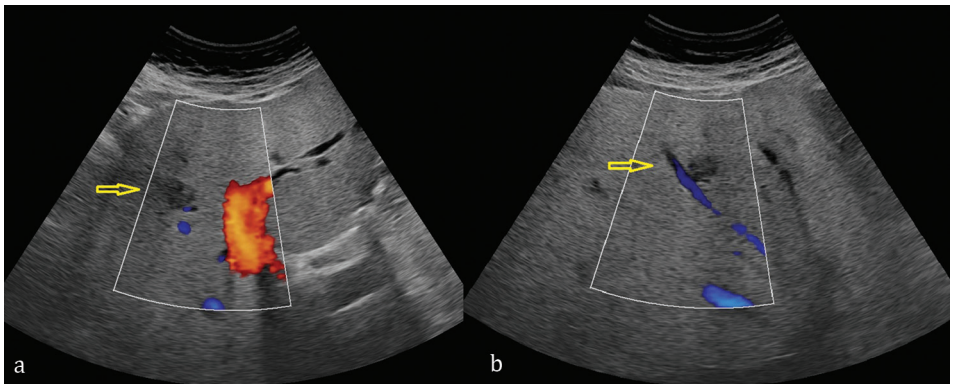


**Fig. 5**. Liver Gaucheroma: a) ultrasound findings: multiple hypo echoic small focal lesion, without mass effect on surrounding vessels.

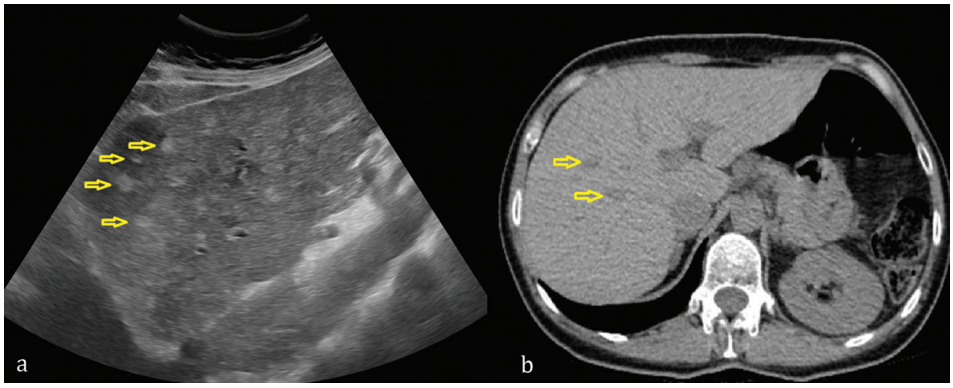


**Fig. 6.** Liver Gaucheromas: a) ultrasound imaging: multiple hyperechoic lesions; b) MRI examination: no specific findings.

**Table I**. Summary of the studies evaluating Gaucheromas

| No. | Author | Total Subjects (No.) | GD type | Localization | Evolution | Therapy |
|---|---|---|---|---|---|---|
| 1 | Mahajan et al. [11] | 1 | 3 | soft tissue-back | diminished | ERT |
| 2 | Yano et al. [12] | 1 | 3 | mesenteric | diminished | SRT |
| 3 | Erdal et al. [13] | 1 | 1 | spleen | N.A. | N.A. |
| 4 | Tseng et al. [14] | 1 | N.A. | multiple abdominal liver and mesenteric lymph node | not changed | ERT |
| 5 | Korula et al. [15] | 1 | 1 | liver | N.A. | ERT |
| 6 | Regenboog et al. [16] | 9/40 | 1 | spleen | N.A. | ERT and SRT |
| 7 | Regenboog et al. [17] | 38/95 | 1 | liver (24) and spleen (23) | N.A. | ERT and SRT |
| 8 | Ivanova et al. [18] | 3/63 | 1 | extraosseous | N.A. | N.A. |
| 9 | Poll et al. [19] | 1 | N.A. | liver | N.A. | N.A. |
| 10 | Lolert et al. [20] | 1/17 | 1 | spleen | N.A. | N.A. |

N.A.: not assessed; ERT: enzyme replacing therapies; SRT: substrate reducing therapies.

high risk in GD patients (low platelets, anemia, spleen size and architectural alterations). Splenectomy is performed nowadays only in selected cases when no response to conventional therapy is expected, compared to the pre-ERT era when splenectomy was frequently used in GD-related thrombocytopenia and anemia (20/74 adult patients in Romania).

**Hepatic Gaucheromas**

Differential diagnosis of liver lesions is often necessary. Focal nodular hyperplasia [17, 19] should be considered. The ultrasound findings are usually a regular shaped mass, with peripheral augmentation of vascular signal and can often produce mass effect (as the main characteristic is a regenerative lesion, with multiple nodules in histological findings) [21]. Hemangiomas, on the other side, are homogenous and hyperechoic most of the times (except the cavernous type with specific appearance) [22]. Doppler signal (or Power Doppler) can ease the differentiation, as hemangiomas tend to have specific vascularization and characteristic behavior in CEUS and CT with contrast. Malignancy is always to be considered in the differential diagnosis, as hepatocellular carcinoma is often described in GD patients [23]. Chronic viral hepatitis B or C (as GD patients required blood transfusions repeatedly before specific treatment), presence of liver involvement concur to a higher risk of liver malignancies. Different from Gaucheromas, hepatocellular carcinoma has a specific malignancy appearance on ultrasound (irregular shape, increased mass effect on the surroundings, shape and size changes in a short period of time) and high specificity of the serum tumor markers (serum alpha-fetoprotein).

In our cases, liver/spleen biopsy had not been performed, as all the presented cases also underwent supplementary imagistic methods (CT/MRI scan) without any malignancy characteristics. Furthermore, the ultrasonographic findings have not changed during the last 5 years of follow-up (twice a year) and no biological examinations suggested otherwise.

**Bone Marrow Gaucheromas**

We only found one patient with a Gaucheroma involving the bone. Although rare, pathological fractures in GD patients are sometimes the first sign of the disease, with histological confirmation after surgery (2 cases from our patients). Ultrasound examination is hardly available (high frequency transducers or continuity solution). Differentiation is to be made with malignancies or callus formation (if examined later). Osteosarcoma tends to be heterogenic, with necrosis, vascular areas and bone destruction or periosteal reaction [24]. Bone Gaucheroma, as reported in our study, is mostly homogeneous, without any vascularization and the bone destruction is limited without any periosteal reaction. Callus formation is also without periosteal reaction, but studied masses are mostly hyperechoic and vascularized at first with later homogenous calcifications [25, 26].

## CONCLUSIONS

Gaucheromas are rare non-malignant tumors that can be found in GD patients if monitored carefully. Ultrasound findings are relevant for Gaucheromas, as malignancy characteristics are not found. MRI evaluation is to complete the imagistic investigation, as histopathological examination is difficult to obtain. Differential diagnosis is crucial in a rare disease patient with any abnormal ultrasound findings. As the Gaucheromas have a heterogenous appearance, both using ultrasound and MRI or computed tomography, periodical imagistic evaluation is mandatory. Ultrasound remains the most accessible and non-invasive method for Gaucheroma monitoring in GD patients. In Romanian GD adult patients, ultrasound findings were similar to the presented literature.

**Conflicts of interest**: None to declare.

**Authors' contributions:** B.A.C. conceived and designed the study. B.A.C. and A.I. collected the data. B.A.C. analyzed the data analysis drafted the manuscript. B.A.C. and A.F.C. searched the literature, selected studies and extracted data.. All authors critically revised the manuscript, approved the final version to be published, and agree to be accountable for all aspects of the work.

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