Ironing out pathophysiological aspects of Gaucher disease

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Imaging characteristics of focal splenic and hepatic lesions in type 1 Gaucher disease

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Abstract

In Gaucher disease (GD) imaging of liver and spleen is part of routine follow-up of GD patients. Focal lesions in both liver and spleen are frequently reported at radiological examinations. These lesions often represent benign accumulations of Gaucher cells, so-called “gaucheroma”, but malignancies, especially hepatocellular carcinoma, are more frequently found in GD as well. We report the imaging characteristics of all focal lesions in liver and spleen in the Dutch GD cohort. Of the 95 GD1 patients, 40% had focal splenic and/or hepatic lesions, associated with more severe GD. Lesions identified as gaucheroma have variable imaging characteristics: hyper- to hypointense on MRI, hyper- or hypoechoic on US and hypodense on computed tomography (CT). Hepatic lesions were classified as simple cysts or haemangioma based upon imaging characteristics. Focal nodular hyperplasia (FNH), gaucheroma and hepatocellular carcinoma (HCC) could not be distinguished by conventional US, CT or MRI. Growth of these lesions and/or characteristics of HCC on dynamic CT or MRI and pathology was used to identify or rule out HCC. We propose a decision-making algorithm including the use of growth and dynamic CT- or MRI-scanning to characterize lesions.
Introduction

Gaucher disease (GD; Online Mendelian Inheritance in Man #230800) is a rare lysosomal storage disorder in which the lysosomal enzyme glucocerebrosidase (GBA1) is deficient. This deficiency leads to accumulation of the glycosphingolipid glucosylceramide, a component of cell membranes [1]. Accumulation takes place in macrophages, which can be engorged with glucosylceramide. The lipid-laden macrophages, Gaucher cells, are mainly found in spleen, liver and bone marrow. Clinical manifestations include hepatosplenomegaly, anemia, thrombocytopenia, leukopenia, bone pain, avascular bone necrosis, pathologic fractures and vertebral compression. The occurrence of symptoms is subject to variety in each affected individual and the onset of symptomatology can occur at any age. GD is classically categorized into three phenotypic variants, of which type 1 (GD1) is the most common [2, 3]. Over the years it has become clear that GD is associated with an increased risk of developing malignancies. Amongst others, hepatocellular carcinoma (HCC), multiple myeloma and other hematological malignancies have been described [4-6].

Since more than two decades, enzyme replacement therapy (ERT) is available for treatment of GD. ERT is able to reduce liver- and spleen volumes and to improve cytopenia and bone disease [7, 8]. Centers of expertise have implemented protocols for follow-up of their patients to assess bone marrow involvement and regular monitoring of hepatosplenomegaly using magnetic resonance imaging (MRI) or ultrasonography (US) is widely applied [9-12]. During these routine assessments, a frequently encountered phenomenon is the appearance of focal splenic and/or hepatic lesions [13]. Some of these lesions are thought to be benign clusters of Gaucher cells, so-called ‘gaucheroma’. However, gaucheroma can show major variance in their imaging characteristics and can be incorrectly considered to be a neoplasm such as lymphoma or HCC [14]. The frequent occurrence of focal lesions in spleen and liver in GD patients leads to a challenge in determining the most appropriate follow-up for each individual.

With this study we aim to provide an overview of the imaging characteristics of different focal splenic and hepatic lesions found in adult GD1 patients in our population. A secondary aim of this paper is to compare disease characteristics of patients with and without focal hepatic or splenic lesions. Based on our data and existing literature, we propose follow-up recommendations to aid in the clinical decision-making in GD1 patients with focal splenic and/or hepatic lesions.
Chapter 6

Methods

The Academic Medical Center in Amsterdam is the center of excellence for GD patients in The Netherlands. We performed a retrospective review of all available imaging reports of 95 adult GD1 patients evaluated at our clinic from 1990 until 2015. All patients were diagnosed with GD based on low glucocerebrosidase activity in peripheral blood leucocytes and genotyping of the GBA1-gene.

Imaging protocols
During follow-up of GD1 patients at our center, liver and spleen volumes are measured at regular intervals both in treated and untreated patients. In the nineties, non-contrast enhanced single slice CT-scanning was used for this purpose, replaced by non-contrast enhanced T1-weighted MRI later on. This latter approach limits radiation exposure and can be obtained directly after the regular bone marrow MRI assessments. The restriction of this MRI-protocol with T1-weighted series only is the limited ability to assess the parenchyma in detail and, when present, characterize focal lesions. In case of incidental hepatic or splenic lesions, ultrasound (US) examination is usually initially performed. Depending on the findings, (multi-phase) CT, MRI or pathologic examinations may follow. Because of the increased risk to develop HCC, we have implemented a protocol to examine all splenectomized GD1 patients with US of the liver every six months.

Data acquisition and analysis
The following parameters were recorded for each patient: gender, genotype, spleen status, pre-treatment severity score index (SSI) [15], pre-treatment chitotriosidase level, pre-treatment liver- and spleen volume, presence of bone complications, site of focal lesions (liver, spleen or both) and imaging modalities performed (US, CT or MRI, either with or without contrast enhancement). Characteristics of GD1 patients at baseline, i.e. before treatment or for untreated patients, the first date of imaging at our center, were compared for groups with and without focal lesions in spleen and/or liver. For statistical calculations SPSS version 22.0 was used (SPSS Inc. Chicago, Illinois, USA). Baseline characteristics of patients are reported in medians and ranges, and in percentages for categorical data. To compare differences between these cohorts, Mann-Whitney U test for continuous data or chi-squared test for categorical outcomes was performed. A p-value of <0.05 was considered statistically significant.
Reported focal lesions in spleen and/or liver were reviewed by an expert panel consisting of two radiologists (O.v.D., I.S.) with expertise in the abdominal imaging field. This expert panel was blinded to radiology and pathology reports. Imaging characteristics of the lesions were recorded per available imaging modality and agreement on the differential diagnosis was obtained. General features of the lesions found are summarized and a comparison of our findings to existing literature is made.

**Results**

Thirty-eight of the 95 GD1 patients (40%) had a focal lesion in liver and/or spleen reported at least once during follow-up. Twenty-three patients (24%) showed focal splenic lesions and in twenty-four patients (25%) hepatic lesions were reported. In nine patients focal lesions were found both in spleen and liver. Table 1 summarizes the baseline patient characteristics of all patients. Patients in the group with focal lesions did not differ from the group without lesions regarding sex, number of splenectomies, age and genotypes. Compared to the 38 patients with focal lesions, the 57 patients without lesions showed a somewhat less severe GD, based on a lower median SSI-score ($p = 0.01$), lower median chitotriosidase levels ($p = 0.035$), lower median spleen volumes ($p = 0.009$) and a lower proportion of patients with a history of bone complications ($p = 0.003$). If we exclude patients with splenic lesions from the analysis, the group with focal liver lesions comprises a statistically significant higher percentage of splenectomized patients as compared to patients without lesions in the liver (50% versus 24%, $p = 0.017$).
Table 1. Baseline characteristics of all patients (with and without focal lesions).

|                            | Focal lesions liver/spleen | No focal lesions liver/spleen | P-value |
|---------------------------|----------------------------|-------------------------------|---------|
| No. of patients (%)       | 38 (40%)                   | 57 (60%)                      | NA      |
| Men, no. (%)              | 20 (53%)                   | 30 (53%)                      | NS      |
| Age in 2016 (years), median (range) | 56.0 (27-92)             | 50.5 (21-82)                  | NS      |
| Splenectomies, no. (%)    | 12 (32%)                   | 17 (30%)                      | NS      |
| SSI-score, median (range) | 7 (2-19)                   | 6 (1-19)                      | 0.01    |
| Chitotriosidase (nmol/ml/hr), median (range) | 31,133 (3,701-98,992)      | 23,080 (2,964-143,458)        | 0.035   |
| Presence of bone complications, no. (%) | 25 (66%)                 | 20 (35%)                      | 0.003   |
| Genotype N370S/L444P, no. (%) | 12 (32%)                  | 22 (39%)                      | NS      |
| Liver volume (ml), median (range) | 2831 (1076-6542)         | 2228 (1213-5814)              | NS      |
| Spleen volume (ml), median (range) | 1688 (145-5358)          | 885 (113-3354)                | 0.009   |

SSI=severity score index, NA not applicable, NS not significant.

Splenic lesions
In twenty-three patients focal lesions of the spleen were described. Twenty patients had multiple splenic lesions. CT-examinations were available in 15, in which splenic lesions all appeared hypodense (see figure 1). Contrast-enhanced CT-images were available in three patients, with one lesion showing slight enhancement of the rim (no. 7). On (non-contrast enhanced) T1-weighted MR-images focal lesions appeared hyperintense in five patients, hypointense in three patients and mixed hypo-/hyperintense signal in four patients. One patient (no. 35) showed hyperintense and mixed signal intensity lesions on T1-weighted images. MRI with contrast performed in one patient (no. 4) showing no contrast enhancement of the focal splenic lesion. T2-weighted MR-images were available in four patients; two patients had hyperintense lesions and in two patients the lesions appeared hypointense. Examples of splenic lesions found on MRI-examination are given in figure 2. US-examinations were reviewed in 15 patients, examples are depicted in figure 3. Focal splenic lesions appeared hyperechoic in six patients, hypoechoic in four patients and mixed signal lesions were noted in three cases. Two patients had multiple lesions of different echogenicity within the spleen. In five patients calcifications in splenic lesions were present. For the majority of lesions, a follow-up of several years was available and no malignant transformation of any of the splenic lesions was observed, nor did splenic lymphoma occur. In addition, while the presence of lymphadenopathy was not within the scope.
of the present study, in none of the patients with splenic or hepatic lesions the presence of lymphadenopathy was reported. No pathologic examinations of splenic lesions were available. In all cases, the most likely diagnosis was gaucheroma. Two splenectomized patients had small, calcified accessory spleens of 10 mm and 13 mm respectively, without signs of gaucheroma. Over time, these accessory spleens did not change with respect to characteristics or size. Table 2 summarizes the imaging characteristics of all splenic lesions.

Figure 1. Examples of CT findings of splenic lesions, suggestive of gaucheroma. A. CT-examination of a 54-years old male patient showing multiple hypodense lesions in the spleen. Note the calcifications (arrow) B. Two hypodensities of the spleen in a 35-years old female.
Figure 2. MRI findings in four GD patients with focal splenic lesions. A. Enlarged spleen with a heterogeneous aspect in a 47-years old GD1 male patient, several focal lesions of mixed signal intensity. B. A 58-years old female patient with a round, mainly hyperintense lesion on T1w image of the spleen. C. Small hyperintense splenic nodule (see arrow) in the spleen of a male patient aged 74 years.
Figure 3. Examples of US findings in GD patients. A. hyperechoic lesion in the spleen of a 29-years old female. Differential diagnosis: haemangioma or gaucheroma (case no.32) B. Two hypodense splenic lesions in a male patient 52 years of age, most likely gaucheroma.
| Patient number | Solitary / Multiple splenic lesions | CT appearance | MRI appearance | Ultrasound appearance | Differential radiological diagnosis |
|----------------|-----------------------------------|---------------|---------------|----------------------|-----------------------------------|
| 1              | Multiple                          | NECT: hypodense, CECT: no enhancement | -              | -                    | Gaucheroma                        |
| 4              | Multiple                          | -             | T1: mixed hypo-/hyperintense, T1C+: no enhancement | Hyperechoic | Gaucheroma                        |
| 6              | Solitary                          | -             | -             | Hyperechoic          | Haemangioma / gaucheroma          |
| 7              | Multiple                          | NECT: hypodense, CECT: slight enhancement of rim of the lesion | - | Hypoechoic with hyperechoic rim | Gaucheroma                        |
| 12             | Multiple                          | NECT: hypodense | -             | -                    | Gaucheroma                        |
| 13             | Multiple                          | -             | T1: mixed hypo-/hyperintense | - | Gaucheroma                        |
| 15             | Multiple                          | NECT: hypodense with calcifications | T1: heterogeneous aspect | Hypoechoic with calcifications | Gaucheroma                        |
| 17             | Multiple                          | NECT: hypodense | T1: hyperintense | Hypoechoic with hyperechoic with hyperechoic rim | Gaucheroma / infarction           |
| 18             | Multiple                          | NECT: hypodense | T1: hypointense | Hypoechoic           | Gaucheroma / infarction           |
| 20             | Multiple                          | NECT: hypodense | -             | Hypoechoic           | Gaucheroma                        |
| 22             | Multiple                          | -             | -             | Hypoechoic with calcifications | Gaucheroma                        |
| 25             | Multiple                          | NECT: hypodense with calcifications | T1: hyperintense with calcifications | - | Gaucheroma                        |
| 28             | Multiple                          | NECT: hypodense | T1: hyperintense | Hypoechoic           | Gaucheroma                        |
| 29             | Multiple                          | -             | -             | Hypoechoic           | Gaucheroma                        |
| 30             | Multiple                          | NECT: hypodense with calcifications | - | Hypoechoic | Gaucheroma                        |
| 31             | Multiple                          | NECT: hypodense | T2: hyperintense | - | Gaucheroma                        |
| 32             | Solitary                          | -             | -             | Hypoechoic           | Hemangioma / gaucheroma           |
| 33             | Multiple                          | NECT: Diffuse hypodense with calcifications | T1: mixed hypo-/hyperintense | - | Gaucheroma                        |
| 34             | Multiple                          | NECT: hypodense | T1: hyperintense, mixed hypo-/hyperintense T2: hypointense | - | Gaucheroma                        |
| 35             | Multiple                          | NECT: hypodense, CECT: no enhancement | T1: hypointense T2: hyperintense | Hypoechoic with hypoechoic center | Gaucheroma                        |
Focal hepatic and splenic lesions in GD

Splenic Lesions
Imaging characteristics

| Patient number | Solitary / Multiple splenic lesions | CT appearance | MRI appearance | Ultrasound appearance | Differential radiological diagnosis |
|---------------|-----------------------------------|---------------|----------------|-----------------------|-----------------------------------|
| 36            | Multiple                          | NECT: hypodense, some with calcifications | -              | -                     | Gaucheroma                        |
| 37            | Multiple                          | -             | T1: hyperintense | Hyperechoic           | Gaucheroma                        |
| 38            | Solitary                          | -             | T2: hypointense  | Hyperechoic           | Gaucheroma                        |

Abbreviations: NECT: non contrast-enhanced CT. CECT: contrast-enhanced CT. T1 C+: contrast enhanced T1 weighted MRI.

Hepatic lesions

Focal hepatic lesions were found in twenty-four patients, of whom twelve were splenectomized. In table 3 a summary of all imaging findings is provided. Examples of imaging findings are depicted in figures 4 and 5. In five patients a radiological diagnosis of simple liver cysts was made. In four patients the distinction between a liver cyst or gaucheroma could not be made based on the imaging examinations. All these lesions had a hypodense appearance on non-contrast-enhanced CT images. Available MRI data showed T1 hypo-intense and T2 hyperintense signal of the lesions.

In seven cases, the presence of a haemangioma was considered. These lesions all fulfilled the typical imaging characteristics of a haemangioma on ultrasonography (hyperechoic, hypervascular), except for one (no. 11) in which the lesion was described as hypoechoic and hypervascular. In this case an ultrasound-guided biopsy of the lesion was performed, because HCC was suspected. This lesion showed arterial enhancement after contrast administration on CT. Pathologic examination proved the lesion to be a gaucheroma.

Focal nodular hyperplasia (FNH) was the main differential diagnosis based on imaging appearance in three patients. This diagnosis was confirmed by pathology examination in one (no. 5). All three lesions showed enhancement on MR imaging after contrast agent administration, but no clear enhancing central scar was noticed in these cases. Two US examinations reported hypoechoic lesions and in one case the lesion was not visible on US.

In two cases, the diagnosis of gaucheroma was made after excluding other possible diagnoses. Both patients had multiple lesions in the liver with a hypodense aspect and...
both showed calcifications in some of the lesions. On ultrasound (data available for one gaucheroma case) the lesions appeared hyperechoic.

Hepatocellular carcinoma was found and confirmed by pathology examination in four patients (no. 2, 14, 19, 27). In one patient (no. 27) the typical HCC characteristics were present on contrast-enhanced CT-images; multiple strongly enhancing lesions, with wash-out of contrast in the delayed phases. In cases 14 and 19 the malignant lesions showed enhancement after contrast agent administration, but wash-out was not detected. The focal lesion in case 14 was not clearly visible on ultrasound examination. Follow-up MRI showed growth of the lesion, which was an indication for surgery. Case 19 had a focal lesion detected on US. Further characterization was performed on dynamic scans and signs of (multifocal) HCC were shown, although wash-out of the lesions was not present. In the fourth case (no.2) no dynamic examinations were available for review. This lesion was hyperechoic on US examination and visible as a hypodense area on non-contrast enhanced CT.
Focal hepatic and splenic lesions in GD

Figure 4. Hepatic lesions found on MRI-scanning (T1-weighted images), indicated by red arrows. A. Hyperintense lesion cranial in liver, differential diagnosis: FNH or Gaucheroma. Patient is a male of 62 years. B. Hypointense lesion, differential diagnosis: hemangioma or Gaucheroma, in a female patient aged 28 years.

Figure 5. Examples of focal lesions on US in livers of GD patients, indicated by white crosses. A. hypoechoic lesion, corresponding to the MRI in figure 4A, in a 62 years old patient. Differential diagnosis: FNH of gaucheroma. B. hyperechoic lesion in the liver of a 32 years old female, based on additional MRI examination, this lesion is thought to be a hemangioma. C. typical aspect of a simple cyst in a 58 years old female.
Table 3. Imaging characteristics of hepatic lesions found on the different imaging modalities.

| Patient number | Solitary / Multiple hepatic lesions | CT appearance | MRI appearance |
|----------------|------------------------------------|---------------|---------------|
| 2              | Solitary                           | NECT: hypodense area | -             |
| 3              | Multiple                           | -             | calcifications |
| 4              | Multiple                           | -             | T1: hypointense |
| 5              | Multiple                           | 1. CECT: arterial enhancement, sharp demarquation and wash-out 2. small cyst | 1. T1C+: enhancement in arterial phase, slight hyperintense signal on diffusion images. Not visible on T1 and T2, no wash-out. |
| 8              | Solitary                           | -             | T1: small demarquated lesion, cyst |
| 9              | Solitary                           | -             | T1: hypointense  T2: hyperintense  T1 C+: sharply demarquated lesion, no contrast enhancement, slight late enhancement peripherally |
| 10             | Multiple                           | NECT: hypodense | T2: Hyperintense |
| 11             | Solitary                           | CECT: arterial and venous enhancement of lesion | -             |
| 14             | Multiple                           | CECT: arterial enhancement, central necrosis | T1: hyperintense  T2: hyperintense  Diffusion: hyperintense  T1 C+: enhancing lesion, no wash-out |
| 15             | Solitary                           | NECT: hypodense lesion (cyst) | -             |
| 16             | Solitary                           | -             | -             |
| 19             | Multiple                           | NECT: hypodense, calcifications | T1: hyperintense  T2: slightly hyperintense  Diffusion: slightly hyperintense  T1 C+: enhancing lesions, no clear wash-out |
| 21             | Multiple                           | NECT: hypodense, calcifications | -             |
| 22             | Solitary                           | -             | T1: round, sharply demarquated, hyperintense  T1 C+: enhancing lesion |
| 23             | Multiple                           | NECT: hypodense | T1: hypointense |
| 24             | Multiple                           | NECT: hypodense | -             |
| 26             | Solitary                           | -             | T1: hypointense |
| 27             | Multiple                           | NECT: hypodense, inhomogeneous liver CECT: strongly enhancing lesions, wash-out | -             |
| 28             | Multiple                           | NECT: hypodense | T1: hypointense |
| 29             | Solitary                           | -             | -             |
| 31             | Multiple                           | NECT: hypodense | T1: hypointense  T2: hyperintense |
| 34             | Multiple                           | -             | T2: hypointense |
| 35             | Solitary                           | -             | T2: hyperintense. Late enhancement |
| 38             | Multiple                           | -             | 1. T2: hyperintense  T1 C+: contrast enhancement, no wash-out  2. some hypointense lesions |
### Table 3: Imaging characteristics of hepatic lesions found on the different imaging modalities.

| Ultrasonound appearance | Imaging characteristics | Differential radiological/pathological diagnosis |
|-------------------------|-------------------------|-------------------------------------------------|
| Hyperechoic             |                         | Hepatocellular carcinoma (pathology examination) |
| Hyperechoic calcifications |                       | Non-specific finding, not of clinical importance |
| Hypoechoic              |                         | Liver cyst                                      |
| 1. not visible          | 1. Focal nodular hyperplasia (pathology examination) |
| 2. some cysts           | 2. Liver cyst          |
| -                       |                         | Liver cyst / gaucheroma                        |
| Hypoechoic              |                         | Haemangioma                                    |
| Hypoechoic, hypervascular |                       | Haemangioma / gaucheroma / hepatocellular carcinoma |
| Heterogeneous signal liver |                       | Pathology examination: Gaucheroma              |
| Hypoechoic              |                         | Liver cyst / gaucheroma                        |
| Heterogeneous signal, hypoechoic lesions | | Hepatocellular carcinoma (pathology examination) |
| Calcifications          |                         | Gaucheroma                                     |
| Hypoechoic              |                         | Focal nodular hyperplasia / gaucheroma         |
| -                       |                         | Gaucheroma / liver cysts                       |
| Hyperechoic nodules; calcifications |                  | Gaucheroma                                     |
| Hyperechoic, sharp demarquation |                | Haemangioma                                    |
| Heterogeneous aspect of liver |                      | Hepatocellular carcinoma (pathology examination) |
| Hypoechoic              |                         | Liver cyst / gaucheroma                        |
| Hyperechoic              |                         | Haemangioma                                    |
| -                       |                         | Haemangioma / gaucheroma / liver cysts         |
| -                       |                         | Liver cysts                                    |
| Hyperechoic              |                         | Haemangioma                                    |
| 1. Hypoechoic           | 1. Focal nodular hyperplasia |
|                         | 2. hemosiderin deposits  |
Discussion

Focal splenic and/or hepatic lesions are a common finding in GD patients, detected by various imaging techniques. Reported prevalence numbers of splenic lesions in GD of different ages range from 18.4% to 33% [14, 16-20]. In contrast to these findings, a study performed in a cohort of pediatric GD patients described focal splenic lesions in 4 out of 103 patients (3.9%) on ultrasound examination [21]. This suggests that with aging, more lesions emerge. The prevalence of focal hepatic lesions is reported to be lower than that of splenic abnormalities. Neudorfer et al found focal lesions in the liver with US examinations in 6.0% of their population [14]. In MRI studies, prevalence rates of hepatic lesions have been described and range from 7% [17] to 20% [19]. Our findings for splenic lesions are in line with these previous reports. In our adult cohort, 24% of patients had a focal lesion in the spleen detected on CT, MRI and/or US. However, the prevalence of focal hepatic lesions of 25% in the Dutch cohort is somewhat higher than reports for gaucheroma frequencies. An explanation could be the fact that we reviewed every reported hepatic lesion, not only gaucheroma, resulting in inclusion of focal liver abnormalities, which are frequently found in the general population [22, 23]. Moreover, as already indicated, our cohort consists of adult GD patients with relatively longstanding disease activity and a substantial percentage of splenectomized patients. Indeed, when the cohort with lesions was compared to the group without lesions, a significant difference between disease severity, represented by a higher percentage of patients with bone complications, higher baseline chitotriosidase levels and higher baseline SSI-scores was found. Apparently, these disease severity characteristics were more important than age, since there was no significant age difference between the groups. It is well known that advanced liver disease is more common in patients after splenectomy and with more severe disease [24, 25]. Apparently, these patients are more prone to develop focal lesions as well. In line with this, in Israeli patients with milder disease, focal liver lesions were reported in only 6.0% of the GD population [14].

Because of the retrospective design of this study, the improving imaging quality and variety of imaging modalities used over the last 25 years, it was not possible to draw firm conclusions regarding the evolution of the lesions over time. This is a limitation of the present study. However, it is fair to say that in general, over a time course of 10 to 20 years, splenic lesions do not disappear, despite impressive reductions in splenic size following treatment with ERT. Neudorfer et al [14] observed no change in splenic lesions in 43.2% of patients following treatment with ERT when comparing 6 month follow-up US with baseline findings. In a pediatric cohort five patients with hepatic or splenic lesions
showed no change in appearance or size as effect of ERT during the follow-up period (mean follow-up 4.5 years) [21]. Contrasting to this finding are the results in pediatric GD patients treated with ERT. In all patients with splenic abnormalities (21%), the lesions resolved during follow-up. These changes were detected in a period from 17 months onwards to more than 4 years [18]. This suggests again a difference between pediatric and adult patients, pointing towards more reversibility of lesions in a younger population. The presence of splenic lesions in GD might influence the response of splenic volume and platelets to therapy. As is shown by Stein et al [16], splenic lesions are associated with a weaker platelet response. Patients with splenic lesions showed less reduction in splenic size as compared to patients without lesions. The presence of focal splenic lesions is proposed as a determinant of response to therapy in GD patients [16].

**Differential diagnosis of splenic lesions**

The general differential diagnosis of splenic lesions comprises inflammatory processes, vascular disorders, hematologic disorders, benign neoplasms and malignant neoplasms [26]. Splenic involvement in lymphoma is the most common splenic malignancy and may be primary or secondary as commonly occurring in Hodgkin and non-Hodgkin lymphoma [27-30]. In GD, lymphoma as well as other hematological malignancies are more frequently found compared to the general population [4, 5, 31, 32]. Thus, it would be helpful to characterize gaucheroma based upon imaging features. The various studies describing imaging features of splenic lesions are summarized in table 4. As shown, imaging characteristics of focal lesions in GD patients are variable. This is probably explained by differences in composition of each lesion, depending on the amount of fibrosis, necrosis, dilated sinusoids and Gaucher macrophages in the lesion. As a result, differentiating between a focal splenic Gaucheroma and a splenic lymphoma solely based on imaging characteristics is not possible. The most important factor is growth of the lesion over time in case of malignancy. Presence of laboratory abnormalities including an M-protein or systemic symptoms such as weight loss, malaise and fever may also be signs of a malignant etiology of the lesion. No malignant lesions of the spleen have been diagnosed in our cohort.

**Differential diagnosis of hepatic lesions and hepatocellular carcinoma**

In 24% of the current population lesions were reported in the liver, including gaucheroma and other abnormalities [22, 33]. A summary of imaging characteristics is given in table 5. As for splenic lesions, gaucheroma of the liver possess variable imaging characteristics and it is therefore difficult to distinguish a gaucheroma from another lesion. Since it is
shown that GD patients have a higher risk of developing HCC [34, 35], which were found in four patients in our cohort, it is important to emphasize the imaging characteristics of these lesions. Unfortunately, as described in the results, not all four HCC cases in GD patients in our cohort did present with typical HCC imaging features, on dynamic CT/MRI examination, which consist of heterogeneous diffuse enhancement in arterial phase and wash-out of contrast agent on delayed images. This indicates the need for watchful surveillance of focal hepatic lesions, especially in patients who underwent previous splenectomy.
### Table 4. Imaging criteria used in diagnosing common splenic lesions.

| Splenic lesions | Diagnosis | References | General characteristics | CT appearance | MRI appearance | US appearance |
|-----------------|-----------|------------|--------------------------|----------------|----------------|---------------|
| Hemangioma      | [26, 36]  | Sharply demarcated lesion. Multiple vascular channels. | NECT: hypodense lesion. CECT: enhancement subject to variety; centripetal enhancement from periphery with persistence on delayed images / mottled enhancement with areas remaining hypodense to normal spleen / immediate homogeneous enhancement. | T1: hypointense. T2: hyperintense. T1 C+: variable enhancement patterns (as in CECT). | | Hypoechoic or hyperechoic. |
| Splenic cyst     | [26, 36]  | Well-defined fluid-filled space. Usually oval or round lesion with a thin wall. | NECT: isodense to water. CECT: no enhancement. | T1: hypointense. T2: hyperintense. T1 C+: no enhancement. | | Anechoic |
| Lymphoma        | [26-30, 36] | May be primary splenic lymphoma or secondary. Multiple lesions or single lesion. | NECT: hypodense, homogeneous lesion. CECT: hypoenhancement of lesion. | T1: isointense. T2: hypo- or isointense. T1 C+: hypoenhancement of lesion. | | Hypoechoic |
| Gaucheroma      | [14, 17-20, 37, 38] | Clusters of Gaucher cells, areas of fibrosis, necrosis, calcifications and iron deposition. | NECT: isodense, hypodense lesion. CECT: enhancement of lesion with hyperdense rim, targetlike lesion. | T1: hypointense, hyperintense, isointense, mixed signal intensity. T2: hypointense, hyperintense, mixed signal intensities. Targetlike lesions (hypointense center and hyperintense rim) T1 C+: peripheral contrast enhancement or heterogeneous internal enhancement. | | Hypoechoic, hyperechoic or mixed echogenicity. |

**Abbreviations:** NECT: non contrast-enhanced CT. CECT: contrast-enhanced CT. T1 C+: contrast enhanced T1 weighted MRI.
| Diagnosis              | References     | General characteristics                                                                 | Hepatic lesions                                | MRI appearance                          | US appearance                                      |
|------------------------|----------------|------------------------------------------------------------------------------------------|------------------------------------------------|-----------------------------------------|--------------------------------------------------|
| Cavernous hemangioma   | [22, 33, 39, 40] | Benign tumor composed of multiple vascular channels<br>Sharply demarcated spherical to ovoid lesion, <10 cm. Giant hemangioma (>10 cm); atypical appearance possible, central fibrous scarring may prevent complete fill in. | NECT: Same density as blood vessels, giant hemangiomas may have central scarring and calcifications.<br>CT: Discontinuous peripheral enhancement, nodular or globular.<br>Progressive fill-in. Areas of enhancement same density as the bloodpool.<br>CECT: Discontinuous peripheral enhancement, nodular or globular.<br>Progressive fill-in. Areas of enhancement same density as the bloodpool. | T1: iso- or hypointense to blood<br>T2: hyperintense<br>T1 C+: Same enhancement pattern as CECT. | Hyperechoic mass with acoustic enhancement (occasionally iso- or hypoechoic)<br>Increased sound transmission |
| Focal Nodular Hyperplasia | [22, 33, 40] | Benign tumor caused by hyperplastic response to localized vascular abnormality<br>Typically in young women<br>Usually lobulated/well circumscribed Central fibrous scar with large vessels. | NECT: well-defined, hypo- or isodense to normal liver<br>CT: hyperdense in arterial phase (except central scar), homogeneous enhancement. In portal and late phases: isoenhancement. Central scar hyperdense. | T1: isointense with hypointense central scar<br>T2: isointense or slightly hyperintense, hyperintense central scar (sometimes hypointense)<br>T1 C+: Same enhancement pattern as CECT. | Non-specific ill-defined isoechoic lesion, occasionally hypo- or hyperchoic.<br>Central scar may be detected as hyperechoic. Color Doppler: spoke-wheel pattern due to central feeding artery with small vessels radiating peripherally. |
| Simple hepatic cyst    | [22, 33] | Benign, congenital, developmental lesion derived from biliary endothelium. Well-defined fluid-filled space<br>Usually oval or round lesion with a thin wall, often multiple. | NECT: isodense to water (-10 to 10 HU)<br>CT: no enhancement | T1: hypointense<br>T2: hyperintense<br>T1 C+: no enhancement | Anechoic |
| Hepatocellular carcinoma | [41, 42] | Characteristic features: hypervascular lesion, mosaic pattern, presence of a tumoral capsule, early arterial enhancement and fast wash-out | NECT: isodense/hypodense ± necrosis, fat, calcification.<br>CT: heterogeneous diffuse enhancement in arterial phase, wash-out on delayed images | T1: hypointense, but may also appear iso- or hyperintense<br>T2: generally hyperintense. Regenerative nodules are hypointense<br>T1 C+: heterogeneous enhancement in arterial phase, wash-out on delayed images | Mixed echogenicity. Peripheral halo, mosaic pattern and lateral shadowing. Color Doppler: hypervascularity and tumor shunting. |
| Gaucheroma             | [19, 21, 43-45] | Clusters of Gaucher cells, areas of fibrosis, necrosis and iron deposition. | NECT: no information available<br>CECT: hyperdense, enhancing lesions | T1: hypointense<br>T2: hyperintense, isointense | Hyperechoic<br>Hypoechoic<br>Targetlike lesions |

Abbreviations: NECT = non-contrast enhanced CT. CECT = contrast-enhanced CT. T1 C+: contrast enhanced T1 weighted MRI.
Follow-up recommendations

In summary, focal lesions in liver or spleen are common in GD1 patients and are not always of benign etiology. In case of focal splenic lesions with no apparent clinical signs or symptoms of a possible lymphoma, a gaucheroma is the most likely diagnosis and routine follow-up is not necessary. Since an isolated splenic lymphoma can be relatively symptom-free, follow-up imaging to detect growth within 6 months could be considered. Needless to say, every indication of growth or resistance to treatment should prompt the clinician to reevaluate the lesions. In figure 6 a proposal of a follow-up algorithm in case of focal liver lesions is provided. Since splenectomized patients are considered to have a higher risk in developing HCC, screening is recommended in accordance with the current guidelines for high risk populations [46].

In case of a lesion >1 cm, further work-up comprising dynamic contrast-enhanced CT- or MRI-scanning is performed. When results of one dynamic contrast-enhanced study are inconclusive, performing a second dynamic contrast-enhanced study should be considered. Lesions that remain indeterminate despite proper imaging work-up require percutaneous imaging-guided biopsy.

In small nodules (< 1cm) one might opt for close imaging surveillance to detect growth. Patients with an intact spleen do not carry the higher HCC-risk. When US characteristics show typical signs of a benign lesion (i.e. anechoic well-defined lesion is a liver cyst) in a GD patient with an intact spleen, follow-up is not necessary. In case of an atypical appearance of the lesion, it is recommended to monitor the lesion frequently, i.e. half-yearly, to detect growth or change in appearance. A much-used practical approach in our center is to discharge patients from follow-up after 2 years of biannual US surveillance without any signs of growth or change of the lesion. In case of any possible sign of malignancy, such as growth of the lesion or the appearance of clinical signs or symptoms (i.e. weight loss, increasing α-fetoprotein levels), we strongly recommend a contrast-enhanced examination to characterize the lesion. Biopsy of a lesion should be considered when results are inconclusive.
Figure 6. Proposal for a follow-up algorithm for focal hepatic lesions in GD patients. *Imaging criteria are described in table 5. In case of an uncertain diagnosis, the 'no'-pathway is followed.
Conclusion

We conclude that splenic and hepatic lesions are common in GD and are more frequent in patients with more severe disease. A gaucheroma is mainly a diagnosis of exclusion, especially in the liver. In our GD1 cohort, followed for several years, splenic lesions were always benign, with gaucheroma being the most likely diagnosis. Lesions in the liver are also gaucheroma, but other lesions occur as well. The variety of imaging characteristics of gaucheroma mandates a rigorous follow-up. A proposal for follow-up of focal hepatic lesions in GD patients is provided, based upon imaging characteristics and growth of the lesion, which aims to detect a malignancy at an early stage.
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