Blood Cells, Molecules and Diseases 60 (2016) 49–57

Contents lists available at ScienceDirect

Blood Cells, Molecules and Diseases

journal homepage: www.elsevier.com/locate/bcmd

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

Martine Regenboog [a,b], Anneloes E. Bohte [a], Inne Somers [a], Otto M. van Delden [a], Mario Maas [a], Carla E.M. Hollak [b,*]

[a] Department of Radiology, Division of Endocrinology and Metabolism, Academic Medical Center, Amsterdam, The Netherlands
[b] Department of Internal Medicine, Division of Endocrinology and Metabolism, Academic Medical Center, Amsterdam, The Netherlands

ARTICLE INFO

*Article history:*
Submitted 28 April 2016
Revised 29 June 2016
Accepted 29 June 2016
Available online 1 July 2016

*Keywords:*
Gaucher disease
Imaging
Gaucheroma
Hepatocellular carcinoma
Follow-up

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.



## 1. 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

*Abbreviations:* GD, Gaucher disease; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging; CT, computed tomography; US, ultrasound; FNH, focal nodular hyperplasia; SSI, severity score index; ERT, enzyme replacement therapy; SRT, substrate reduction therapy.

* Corresponding author at: Department of Internal Medicine/Endocrinology and Metabolism, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.
*E-mail address:* c.e.hollak@amc.nl (C.E.M. Hollak).

http://dx.doi.org/10.1016/j.bcmd.2016.06.009
1079-9796/

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.

## 2. 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.

### 2.1. 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.

### 2.2. 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.

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

| | 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/h), median (range) | 31,133 (3701–98,992) | 23,080 (2964–143,458) | 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 |

### 3.1. 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 Fig. 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 Fig. 2. US-examinations were reviewed in 15 patients, examples are depicted in Fig. 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.

### 3.2. Hepatic lesions

Focal hepatic lesions were found in twenty-four patients, of whom twelve were splenectomized. In Table 3 a summary of all imaging