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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.

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.

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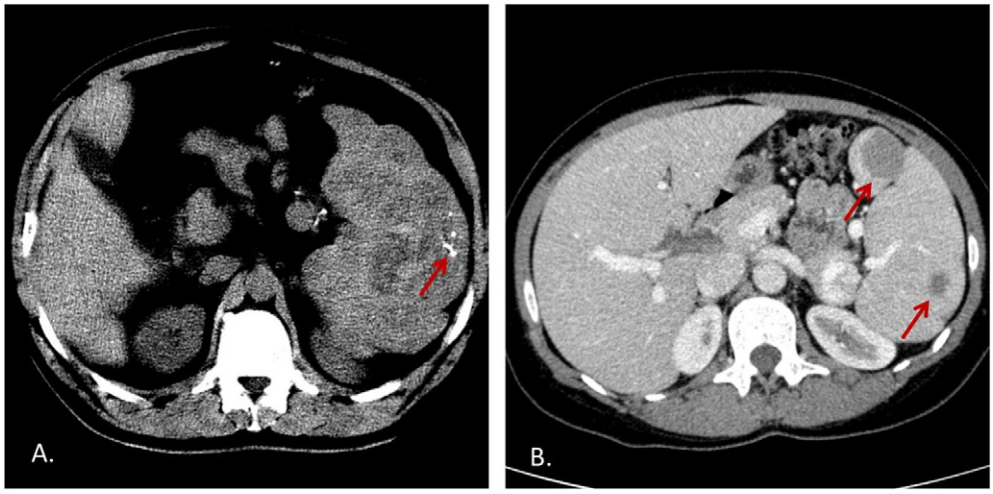

Fig. 1. Examples of CT findings of splenic lesions, suggestive of gaucheroma. A. CT-examination of a 54-years old male patient showing multiple hypodense lesions in the spleen. Note the calcifications (arrow) B. Two hypodensities of the spleen in a 35-years old female.

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

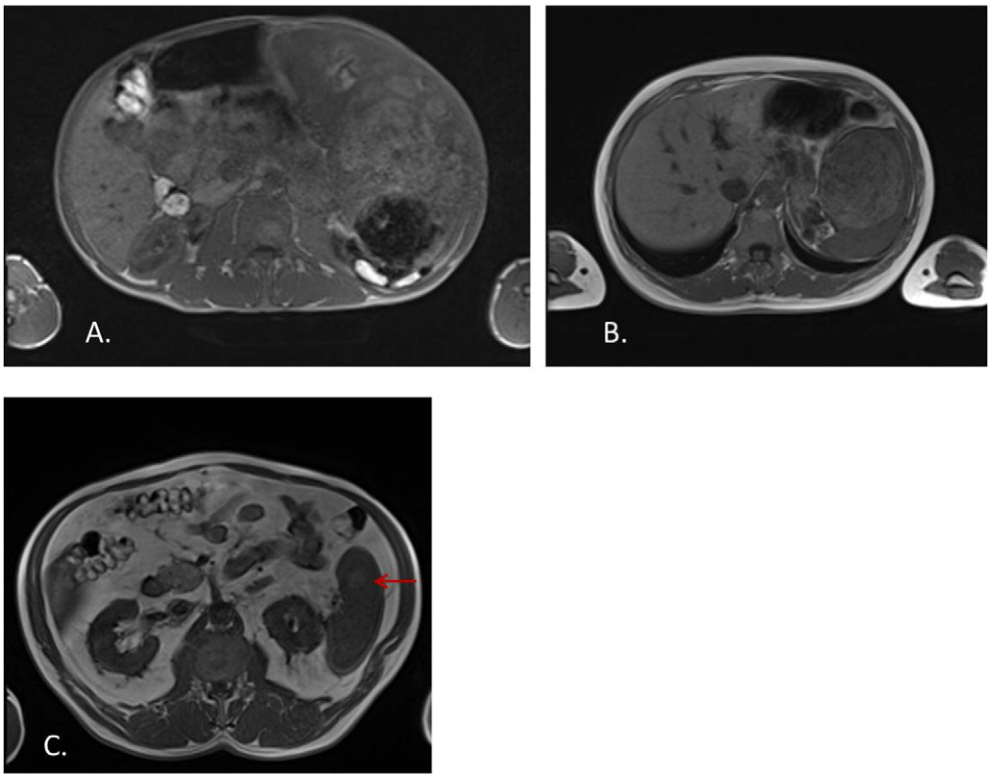

Fig. 2. MRI findings in four GD patients with focal splenic lesions. A. Enlarged spleen with a heterogeneous aspect in a 47-years old GD1 male patient, several focal lesions of mixed signal intensity. B. A 58-years old female patient with a round, mainly hyperintense lesion on T1w image of the spleen. C. Small hyperintense splenic nodule (see arrow) in the spleen of a male patient aged 74 years.

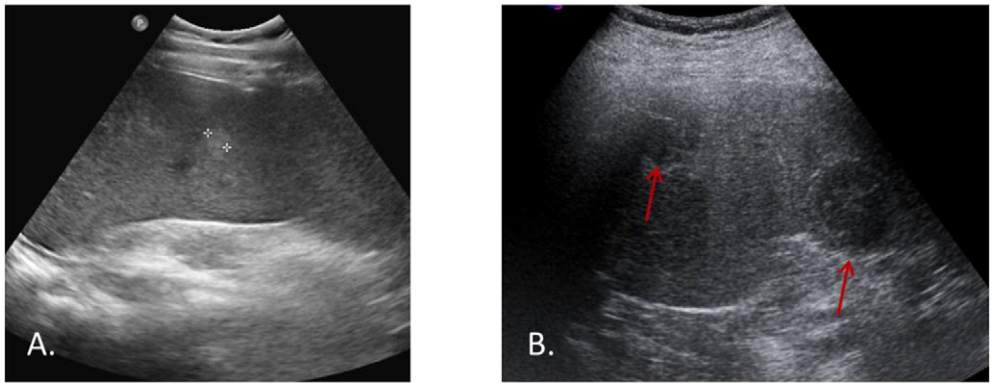

Fig. 3. Examples of US findings in GD patients. A. hyperechoic lesion in the spleen of a 29-years old female. Differential diagnosis: haemangioma or gaucheroma (case no.32) B. Two hypodense splenic lesions in a male patient 52 years of age, most likely gaucheroma.

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%, $p = 0.017$).

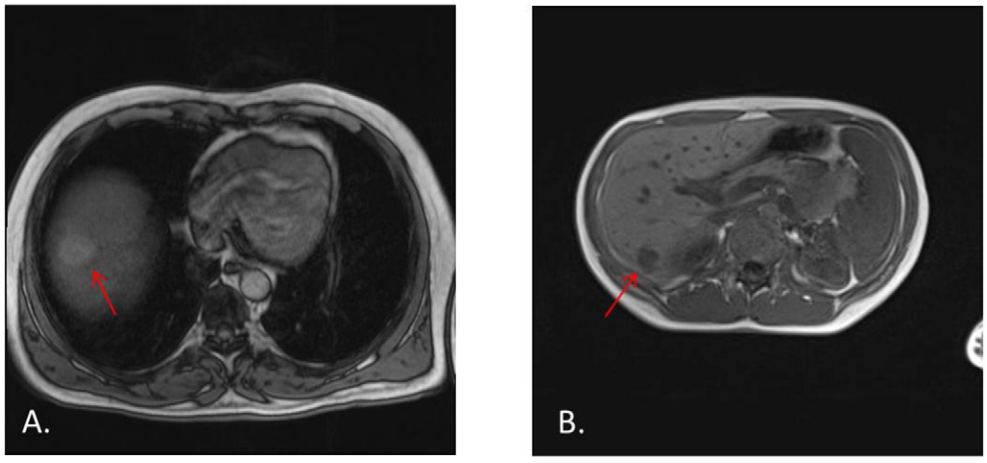

Fig. 4. Hepatic lesions found on MRI-scanning (T1-weighted images), indicated by red arrows. A. Hyperintense lesion cranial in liver, differential diagnosis: FNH or Gaucheroma. Patient is a male of 62 years. B. Hypointense lesion, differential diagnosis: hemangioma or Gaucheroma, in a female patient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

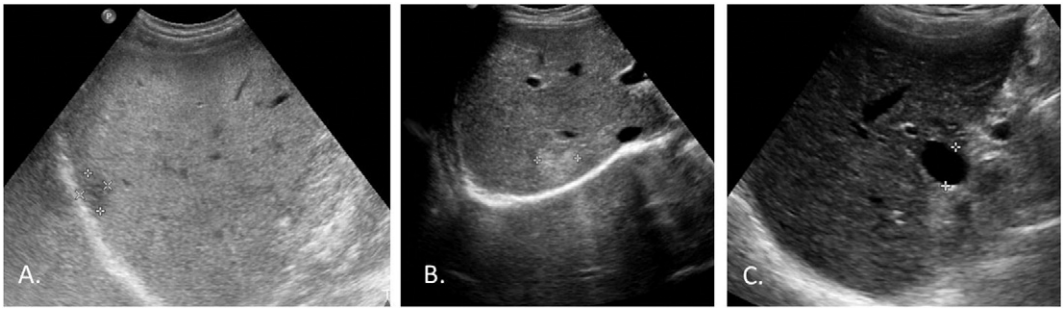

Fig. 5. Examples of focal lesions on US in livers of GD patients, indicated by white crosses. A. hypoechoic lesion, corresponding to the MRI in Fig. 4A, in a 62 years old patient. Differential diagnosis: FNH of gaucheroma. B. Hyperechoic lesion in the liver of a 32 years old female, based on additional MRI examination, this lesion is thought to be a hemangioma. C. Typical aspect of a simple cyst in a 58 years old female.

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.

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

3.2. Hepatic lesions

Focal hepatic lesions were found in twenty-four patients, of whom twelve were splenectomized. In Table 3 a summary of all imaging findings is provided. Examples of imaging findings are depicted in Figs. 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

Table 2
Imaging characteristics of splenic lesions found on the different imaging modalities. Abbreviations: NECT: non contrast-enhanced CT. CECT: contrast-enhanced CT. T1 C+: contrast enhanced T1 weighted MRI.

Splenic lesions					
Imaging characteristics					
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	Hyperechoic Hypoechoic with hyperechoic rim	Gaucheroma/infarction
18	Multiple	NECT: hypodense	T1: hypointense	Hyperechoic Hypoechoic	Gaucheroma/infarction
20	Multiple	NECT: hypodense	–	Hyperechoic	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	–	–	Hyperechoic Isoechoic	Gaucheroma
30	Multiple	NECT: hypodense with calcifications	–	Hypoechoic	Gaucheroma
31	Multiple	NECT: hypodense	T2: hyperintense	–	Gaucheroma
32	Solitary	–	–	Hyperechoic	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	Hyperechoic with hypoechoic center	Gaucheroma
36	Multiple	NECT: hypodense, some with calcifications	–	–	Gaucheroma
37	Multiple	–	T1: hyperintense	Hyperechoic	Gaucheroma
38	Solitary	–	T2: hypointense	Hyperechoic	Gaucheroma

examination and visible as a hypodense area on non-contrast enhanced CT.

4. 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

Table 3
Imaging characteristics of hepatic lesions found on the different imaging modalities. Abbreviations: NECT: non contrast-enhanced CT. CECT: contrast-enhanced CT. T1 C+: contrast enhanced T1 weighted MRI.

Hepatic lesions					
Imaging characteristics					
Patient number	Solitary/Multiple hepatic lesions	CT appearance	MRI appearance	Ultrasound appearance	Differential radiological/pathological diagnosis
2	Solitary	NECT: hypodense area	–	Hyperechoic	Hepatocellular carcinoma (pathology examination)
3	Multiple	–	Calcifications	Calcifications	Non-specific finding, not of clinical importance
4	Multiple	–	T1: hypointense	Hypoechoic	Liver cysts
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.	1. not visible 2. some cysts	1. Focal nodular hyperplasia (pathology examination) 2. Liver cysts
8	Solitary	–	T1: small demarquated lesion, cyst	–	Liver cyst
9	Solitary	–	T1: hypointense T2: hyperintense. T1 C+: sharply demarquated lesion, no contrast enhancement, slight late enhancement peripherally	Hyperechoic	Haemangioma/gaucheroma
10	Multiple	NECT: hypodense	T2: Hyperintense	Hypoechoic	Liver cyst/gaucheroma
11	Solitary	CECT: arterial and venous enhancement of lesion	–	Hypoechoic, hypervascular	Haemangioma/gaucheroma/hepatocellular carcinoma Pathology examination: gaucheroma
14	Multiple	CECT: arterial enhancement, central necrosis	T1: hyperintense T2: hyperintense Diffusion: hyperintense T1 C+: enhancing lesion, no wash-out	Heterogeneous signal liver	Hepatocellular carcinoma (pathology examination)
15	Solitary	NECT: hypodense lesion (cyst)	–	Hypoechoic	Liver cyst
16	Solitary	–	–	Hyperechoic	Haemangioma
19	Multiple	NECT: hypodense, calcifications	T1: hyperintense T2: slightly hyperintense Diffusion: slightly hyperintense T1 C+: enhancing lesions, no clear wash-out	Heterogeneous signal liver, hypoechoic lesions	Hepatocellular carcinoma (pathology examination)
21	Multiple	NECT: hypodense, calcifications	–	Calcifications	Gaucheroma
22	Solitary	–	T1: round, sharply demarquated, hyperintense T1 C+: enhancing lesion	Hypoechoic	Focal nodular hyperplasia/gaucheroma
23	Multiple	NECT: hypodense	T1: hypointense	–	Gaucheroma/liver cysts
24	Multiple	NECT: hypodense	–	Hyperechoic nodules; calcifications	Gaucheroma
26	Solitary	–	T1: hypointense	Hyperechoic, sharp demarquation	Haemangioma
27	Multiple	NECT: hypodense, inhomogeneous liver CECT: strongly enhancing lesions, wash-out	–	Heterogeneous aspect of liver	Hepatocellular carcinoma (pathology examination)
28	Multiple	NECT: hypodense	T1: hypointense	Hypoechoic	Liver cysts/gaucheroma
29	Solitary	–	–	Hyperechoic	Haemangioma
31	Multiple	NECT: hypodense	T1: hypointense T2: hyperintense	–	Haemangioma/gaucheroma/liver cysts
34	Multiple	–	T2: hypointense	–	Liver cysts
35	Solitary	–	T2: hyperintense. Late enhancement	Hyperechoic	Haemangioma
38	Multiple	–	1. T2: hyperintense T1 C+: contrast enhancement, no wash-out 2. some hypointense lesions	1. Hypoechoic	1. Focal nodular hyperplasia 2. hemosiderin deposits

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 >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].

4.1. 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

Table 4
Imaging criteria used in diagnosing common splenic lesions. Abbreviations: NECT: non contrast-enhanced CT. CECT: contrast-enhanced CT. T1 C+: contrast enhanced T1 weighted MRI.

	Splenic lesions				
Diagnosis	References	General characteristics	CT appearance	MRI appearance	US appearance
Hemangioma	[26,36]	Sharply demarcated lesion Multiple vascular channels	NECT: hypodense 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: hypo- or isointense 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 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 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

Table 5
Imaging criteria used in diagnosing common hepatic lesions. Abbreviations: NECT: non-contrast enhanced CT. CECT: contrast-enhanced CT. T1 C+: contrast enhanced T1 weighted MRI.

	Hepatic lesions				
Diagnosis	References	General characteristics	CT appearance	MRI appearance	US appearance
Cavernous hemangioma	[22,33,39,40]	Benign tumor composed of multiple vascular channels 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. CECT: Discontinuous peripheral enhancement, nodular or globular. Progressive fill-in. Areas of enhancement same density as the bloodpool.	T1: iso- or hypointense to blood T2: hyperintense T1 C+: Same enhancement pattern as CECT.	Hyperechoic mass with acoustic enhancement (occasionally iso- or hypoechoic) Increased sound transmission
Focal nodular hyperplasia	[22,33,40]	Benign tumor caused by hyperplastic response to localized vascular abnormality Typically in young women Usually lobulated/well circumscribed Central fibrous scar with large vessels.	NECT: well-defined, hypo- or isodense to normal liver CECT: hyperdense in arterial phase (except central scar), homogeneous enhancement. In portal and late phases: isoenhancement. Central scar hyperdense.	T1: isointense with hypointense central scar T2: isointense or slightly hyperintense, hyperintense central scar (sometimes hypointense) T1 C+: Same enhancement pattern as CECT.	Non-specific ill-defined isoechoic lesion, occasionally hypo- or hyperechoic. 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 Usually oval or round lesion with a thin wall, often multiple.	NECT: isodense to water (−10 to 10 HU) CECT: no enhancement	T1: hypointense T2: hyperintense 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. CECT: heterogeneous diffuse enhancement in arterial phase, wash-out on delayed images	T1: hypointense, but may also appear iso- or hyperintense T2: generally hyperintense. Regenerative nodules are hypointense 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 CECT: hyperdense, enhancing lesions	T1: hypointense T2: hyperintense, isointense	Hyperechoic Hypoechoic Targetlike lesions

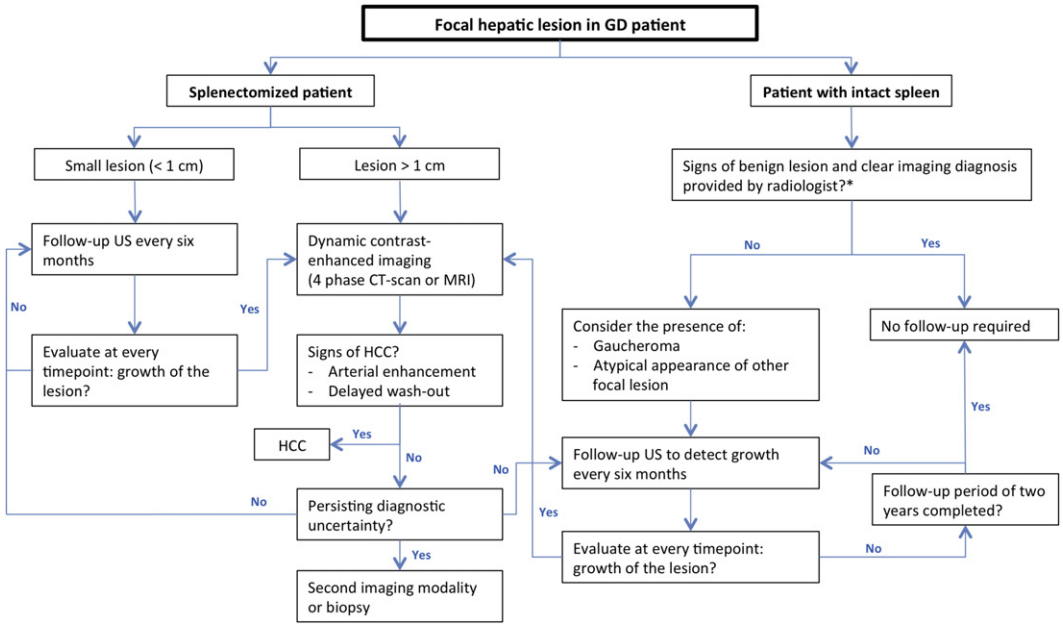

Fig. 6. Proposol for follow-up algorithm for focal hepatic lesions in GD patients. *Imaging criteria are described in Table 5. In case of an uncertain diagnosis, the 'no'-pathway is followed.

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.

4.2. 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.

4.3. 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 Fig. 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 (<1 cm) 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.

5. 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.

Authorship contributions

MR and AEB performed the data acquisition and analysis and wrote the manuscript. IS and OMvD scored the imaging findings. All authors revised the manuscript and approved the final version.

Conflicts of interest

CEMH declares that over the last 3 years, she has received reimbursement of travel and accommodation for serving at Shire's charitable program. MM is a consultant for Genzyme. The Academic Medical Center has received educational and research grants from Genzyme and Shire and receives support for Registries. MR, AEB, IS and OMvD declare no conflicts of interest.

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References

[1] R.O. Brady, J.N. Kanfer, D. Shapiro, Metabolism of glucocerebrosides. II. Evidence of an enzymatic deficiency in Gaucher's disease, Biochem. Biophys. Res. Commun. 18 (1965) 221–225.
[2] T.M. Cox, J.P. Schofield, Gaucher's disease: clinical features and natural history, Baillieres Clin. Haematol. 10 (1997) 657–689.
[3] G.A. Grabowski, G.A. Petsko, E.H. Kolodny, Gaucher Disease, in: D. Valle, A.L. Beaudet, B. Vogelstein, K. Kinzler, S.E. Antonarakis, A. Ballabio (Eds.), The Online Metabolic & Molecular Bases of Inherited Disease, McGraw-Hill, New York, 2010.
[4] M. de Fost, S. Vom Dahl, G.J. Weverling, N. Brill, S. Brett, D. Haussinger, C.E. Hollak, Increased incidence of cancer in adult Gaucher disease in Western Europe, Blood Cells Mol. Dis. 36 (2006) 53–58.
[5] M. Arends, L. van Dussen, M. Biegstraaten, C.E. Hollak, Malignancies and monoclonal gammopathy in Gaucher disease; a systematic review of the literature, Br. J. Haematol. 161 (2013) 832–842.
[6] P.K. Mistry, T. Taddei, S. vom Dahl, B.E. Rosenbloom, Gaucher disease and malignancy: a model for cancer pathogenesis in an inborn error of metabolism, Crit. Rev. Oncog. 18 (2013) 235–246.
[7] N.W. Barton, R.O. Brady, J.M. Dambrosia, A.M. Di Bisceglie, S.H. Doppelt, S.C. Hill, H.J. Mankin, G.J. Murray, R.I. Parker, C.E. Argoff, et al., Replacement therapy for inherited enzyme deficiency–macrophage-targeted glucocerebrosidase for Gaucher's disease, N. Engl. J. Med. 324 (1991) 1464–1470.
[8] N.J. Weinreb, J. Goldblatt, J. Villalobos, J. Charrow, J.A. Cole, M. Kerstenetzky, S. vom Dahl, C. Hollak, Long-term clinical outcomes in type 1 Gaucher disease following 10 years of imiglucerase treatment, J. Inherit. Metab. Dis. 36 (2013) 543–553.
[9] A. Zimran, How I treat Gaucher disease, Blood 118 (2011) 1463–1471.
[10] J. Charrow, J.A. Esplin, T.J. Gribble, P. Kaplan, E.H. Kolodny, G.M. Pastores, C.R. Scott, R.S. Wappner, N.J. Weinreb, J.S. Wisch, Gaucher disease: recommendations on diagnosis, evaluation, and monitoring, Arch. Intern. Med. 158 (1998) 1754–1760.
[11] N.J. Weinreb, M.C. Aggio, H.C. Andersson, G. Andria, J. Charrow, J.T. Clarke, A. Erikson, P. Giraldo, J. Goldblatt, C. Hollak, H. Ida, P. Kaplan, E.H. Kolodny, P. Mistry, G.M. Pastores, R. Pires, A. Prakash-Cheng, B.E. Rosenbloom, C.R. Scott, E. Sobreira, A. Tylki-Szymanska, A. Vellodi, S. vom Dahl, R.S. Wappner, A. Zimran, International Collaborative Gaucher Group, Gaucher disease type 1: revised recommendations on evaluations and monitoring for adult patients, Semin. Hematol. 41 (2004) 15–22.
[12] W.L. Simpson, G. Hermann, M. Balwani, Imaging of Gaucher disease, World J. Radiol. 6 (2014) 657–668.
[13] R.E. Lee, The pathology of Gaucher disease, Prog. Clin. Biol. Res. 95 (1982) 177–217.
[14] O. Neudorfer, I. Hadas-Halpern, D. Elstein, A. Abrahamov, A. Zimran, Abdominal ultrasound findings mimicking hematological malignancies in a study of 218 Gaucher patients, Am. J. Hematol. 55 (1997) 28–34.
[15] A. Zimran, A. Kay, T. Gelbart, P. Garver, D. Thurston, A. Saven, E. Beutler, Gaucher disease. Clinical, laboratory, radiologic, and genetic features of 53 patients, Medicine 71 (1992) 337–353.
[16] P. Stein, A. Malhotra, A. Haims, G.M. Pastores, P.K. Mistry, Focal splenic lesions in type I Gaucher disease are associated with poor platelet and splenic response to macrophage-targeted enzyme replacement therapy, J. Inherit. Metab. Dis. 33 (2010) 769–774.
[17] M.R. Terk, J. Esplin, K. Lee, G. Magre, P.M. Colletti, MR imaging of patients with type 1 Gaucher's disease: relationship between bone and visceral changes, Am. J. Roentgenol. 165 (1995) 599–604.
[18] S. Chippington, K. McHugh, A. Vellodi, Splenic nodules in paediatric Gaucher disease treated by enzyme replacement therapy, Pediatr. Radiol. 38 (2008) 657–660.
[19] S.C. Hill, B.M. Damaska, A. Ling, K. Patterson, A.M. Di Bisceglie, R.O. Brady, N.W. Barton, Gaucher disease: abdominal MR imaging findings in 46 patients, Radiology 184 (1992) 561–566.
[20] S.C. Hill, J.W. Reinig, J.A. Barranger, J. Fink, T.H. Shawker, Gaucher disease: sonographic appearance of the spleen, Radiology 160 (1986) 631–634.
[21] M. Patlas, I. Hadas-Halpern, A. Abrahamov, D. Elstein, A. Zimran, Spectrum of abdominal sonographic findings in 103 pediatric patients with Gaucher disease, Eur. Radiol. 12 (2002) 397–400.
[22] T.E. Kaltenbach, P. Engler, W. Kratzer, S. Oeztuerk, T. Seufferlein, M.M. Haenle, T. Graeter, Prevalence of benign focal liver lesions: ultrasound investigation of 45,319 hospital patients, Abdom. Radiol. 41 (2016) 25–32.
[23] C.F. Dietrich, M. Sharma, R.N. Gibson, D. Schreiber-Dietrich, C. Jenssen, Fortuitously discovered liver lesions, World J. Gastroenterol. 19 (2013) 3173–3188.
[24] A.E. Bohte, L. van Dussen, E.M. Akkerman, A.J. Nederveen, R. Sinkus, P.L. Jansen, J. Stoker, C.E. Hollak, Liver fibrosis in type I Gaucher disease: magnetic resonance imaging, transient elastography and parameters of iron storage, PLoS One 8 (2013), e57507.
[25] R.H. Lachmann, D.G. Wight, D.J. Lomas, N.C. Fisher, J.P. Schofield, E. Elias, T.M. Cox, Massive hepatic fibrosis in Gaucher's disease: clinico-pathological and radiological features, QJM 93 (2000) 237–244.
[26] K.M. Elsayes, V.R. Narra, G. Mukundan, J.S. Lewis Jr., C.O. Menias, J.P. Heiken, MR imaging of the spleen: spectrum of abnormalities, Radiographics 25 (2005) 967–982.
[27] D.M. Warshauer, H.L. Hall, Solitary splenic lesions, Semin. Ultrasound CT MR 27 (2006) 370–388.
[28] K. Kishimoto, T. Koyama, Y. Kigami, H. Kobayashi, K. Akuta, K. Ito, N. Matsunaga, Primary splenic malignant lymphoma associated with hepatitis C virus infection, Abdom. Imaging 26 (2001) 55–58.
[29] A.H. Dachman, J.L. Buck, J. Krishnan, N.S. Aguilera, P.C. Buetow, Primary non-Hodgkin's splenic lymphoma, Clin. Radiol. 53 (1998) 137–142.
[30] K. Bhatia, A. Sahdev, R.H. Reznek, Lymphoma of the spleen, Semin. Ultrasound CT MR 28 (2007) 12–20.
[31] N.J. Weinreb, R.E. Lee, Causes of death due to hematological and non-hematological cancers in 57 US patients with type 1 Gaucher disease who were never treated with enzyme replacement therapy, Crit. Rev. Oncog. 18 (2013) 177–195.
[32] T.H. Taddei, K.A. Kacena, M. Yang, R. Yang, A. Malhotra, M. Boxer, K.A. Aleck, G. Rennert, G.M. Pastores, P.K. Mistry, The underrecognized progressive nature of N370S Gaucher disease and assessment of cancer risk in 403 patients, Am. J. Hematol. 84 (2009) 208–214.
[33] L. Chiche, J.P. Adam, Diagnosis and management of benign liver tumors, Semin. Liver Dis. 33 (2013) 236–247.
[34] R. Xu, P. Mistry, G. McKenna, S. Emre, T. Schiano, M. Bu-Ghanim, G. Levi, M.I. Fiel, Hepatocellular carcinoma in type 1 Gaucher disease: a case report with review of the literature, Semin. Liver Dis. 25 (2005) 226–229.
[35] Z. Erjavec, C.E. Hollak, E.G. de Vries, Hepatocellular carcinoma in a patient with Gaucher disease on enzyme supplementation therapy, Ann. Oncol. 10 (1999) 243.
[36] A. Kamaya, S. Weinstein, T.S. Desser, Multiple lesions of the spleen: differential diagnosis of cystic and solid lesions, Semin. Ultrasound CT MR 27 (2006) 389–403.
[37] T.O. Kalayci, G. Erdem, R. Kutlu, A. Kahraman, A. Alkan, Diffusion-weighted magnetic resonance imaging and magnetic resonance spectroscopy features of abdominal viscera in a patient with Gaucher's disease, Malays. J. Med. Sci. 21 (2014) 89–93.
[38] D. Chatelain, M.P. Bralet, J. Briere, C. Degott, J.F. Flejou, Multiple splenic nodules revealing Gaucher's disease, Histopathology 40 (2002) 203–204.
[39] T.K. Kim, E. Lee, H.J. Jang, Imaging findings of mimickers of hepatocellular carcinoma, Clin. Mol. Hepatol. 21 (2015) 326–343.
[40] A.P. Matos, F. Velloni, M. Ramalho, M. AlObaidy, A. Rajapaksha, R.C. Semelka, Focal liver lesions: practical magnetic resonance imaging approach, World J. Hepatol. 7 (2015) 1987–2008.
[41] J.Y. Choi, J.M. Lee, C.B. Sirlin, CT and MR imaging diagnosis and staging of hepatocellular carcinoma: part I. Development, growth, and spread: key pathologic and imaging aspects, Radiology 272 (2014) 635–654.
[42] T. Murakami, Y. Imai, M. Okada, T. Hyodo, W.J. Lee, M.J. Kim, T. Kim, B.I. Choi, Ultrasonography, computed tomography and magnetic resonance imaging of hepatocellular carcinoma: toward improved treatment decisions, Oncology 81 (Suppl. 1) (2011) 86–99.
[43] M. Patlas, I. Hadas-Halpern, C. Reinus, A. Zimran, D. Elstein, Multiple hypoechoic hepatic lesions in a patient with Gaucher disease, J. Ultrasound Med. 21 (2002) 1053–1055.
[44] L.W. Poll, S. Vom Dahl, Image of the month. Hepatic gaucheroma mimicking focal nodular hyperplasia, Hepatology 50 (2009) 985–986.
[45] I. Hadas-Halpern, M. Deeb, A. Abrahamov, A. Zimran, D. Elstein, Gaucher disease: spectrum of sonographic findings in the liver, J. Ultrasound Med. 29 (2010) 727–733.
[46] F.A. Eskens, K.J. van Erpecum, K.P. de Jong, O.M. van Delden, H.J. Klumpen, C. Verhoef, P.L. Jansen, M.A. van den Bosch, A. Mendez Romero, J. Verheij, E. Bloemena, R.A. de Man, Hepatocellular carcinoma: Dutch guideline for surveillance, diagnosis and therapy, Neth. J. Med. 72 (2014) 299–304.