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Case Report

Focal hepatic lesions in acid sphingomyelinase deficiency: Differential diagnosis between foamy macrophages aggregates and malignancy

Annalisa Sechi [a,*], Alessandro Vit [b], Claudio Avellini [c], Andrea Dardis [a], Andrea Pellegrin [b], Maurizio Scarpa [a], Bruno Bembi [a]

[a] Regional Coordinating Center for Rare Diseases, University Hospital of Udine, Udine, Italy
[b] Division of Vascular and Interventional Radiology, University Hospital of Udine, Udine, Italy
[c] Institute of Pathological Anatomy, University Hospital of Udine, Udine, Italy

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ABSTRACT

Acid sphingomyelinase deficiency (ASMD) is a rare metabolic disorder due to biallelic mutation in the SMPD1 gene. The defect leads to the accumulation of sphingomyelin within the cells of the reticulo-endothelial system, particularly in the spleen, liver, lungs, and bone marrow causing hepato-splenomegaly, lung disease and hematological abnormalities. At present, data on abdominal imaging in ASMD are limited. Here we describe the characteristics of focal liver lesions observed in a 30 years old female. During the Magnetic Resonance follow up an increase in number and size of the lesions, showing T1 hypointensity and T2 hyperintensity with contrast enhancement, was observed. Contrast enhanced ultrasound evidenced rapid wash-in and steady isoecogenicity without appreciable wash-out at 80 seconds. The main lesion was biopsied to rule out the presence of a hepatocellular carcinoma, and showed to be a benign foamy macrophages aggregate. In this report, we discuss the possible pathogenesis of focal hepatic lesions in ASMD and their differential diagnosis.

1. Introduction

Acid sphingomyelinase deficiency (ASMD) (OMIM# 607616) is an autosomal recessive lysosomal storage disorder, due to pathogenetic variants in the *SMPD1* gene. The consequent defect in the degradation of sphingomyelin within the lysosomes leads to the accumulation of this sphingolipid in different organs and tissues, especially in the reticulo-endothelial system. Epidemiologically, ASMD is a rare disease with an estimated incidence of 0.5-2:100.000 living births [1].

The phenotype of ASMD occurs along a continuum between the severe early onset form, or infantile neurovisceral form (Niemann Pick disease type A) and the later onset, chronic visceral form (Niemann Pick disease type B). Clinical manifestations of chronic visceral ASMD include hepato-splenomegaly, thrombocytopenia, interstitial lung disease and dyslipidemia, while central neurological symptoms, typically present in the neurovisceral form, are usually absent [2–4].

Typically ASMD presents in infancy or childhood, however, the diagnosis of milder forms can be delayed until adulthood. Notably, splenomegaly is often the first sign of the disease, accompanied by low platelet count and less frequently anemia and leukopenia [5]. When performed, the bone marrow aspirate typically shows numerous foamy cells with cytoplasm filled with small vacuoles, and sea blue histiocytes [6,7]. Pulmonary function tests evidence a restrictive disease in the vast majority of adult patients [8]. Dyslipidemia is often present with high total cholesterol, increased low-density lipoproteins (LDL), high triglycerides, and decreased high-density lipoproteins (HDL). Hepatic involvement is characterized by liver enlargement that could be as impressive as the splenomegaly, due to the accumulation of lipid-laden macrophages. Liver function tests are usually slightly abnormal, with mild increase of transaminases and bilirubin [9,10].

Considering the rarity of the disease, data on abdominal imaging in patients with ASMD are still scarce, although periodic computer tomography (CT) or magnetic resonance (MR) of the abdomen are recommended to monitor disease progression in the long term follow up [11].

In this paper, we report a clinical case of a splenectomized patient affected by ASMD who presented focal atypical hepatic lesions, one of which was biopsied to rule out the presence of a hepatocellular carcinoma (HCC) and showed to be a benign foamy macrophages aggregate. Similar lesions have been described in patients suffering from Gaucher

* Corresponding author at: Regional Coordinating Center for Rare Diseases, University Hospital of Udine, p.zzale SM della Misericordia 15, 33100 Udine, Italy.
E-mail address: annalisa.sechi@asufc.sanita.fvg.it (A. Sechi).

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disease, a different lysosomal lipid storage disorder due to the deficiency of glucocerebrosidase, in which the specific foamy cells, called Gaucher cells, can conglomerate forming tumor-like nodules named Gaucheromas by some authors [12]. As in ASMD, the macrophages are the primary storage cells in Gaucher disease, with hepatosplenomegaly and bone marrow infiltration among the main clinical manifestations [13].

2. Case report

A 30 years old woman affected by ASMD was admitted to the Regional Coordinatoing Center for Rare Diseases (RCCRD) of the University Hospital of Udine, to undergo blood tests and imaging studies for the regular annual follow up of the disease.

The patient had been diagnosed at the age of 21, after being splenectomized for a suspect of splenic lymphoma, following the detection of splenomegaly and nodular lesions showing arterial-phase enhancement with late parenchymal phase wash-out. The histological analysis of the spleen and a bone marrow biopsy showed the presence of foamy cells raising the suspicion of ASMD [14]. The diagnosis was then confirmed by the presence of reduced ASM activity in leucocytes and the presence of two pathogenetic variants in compound heterozygosity in the SMPD1 gene: [c.1828C>T (p.R610C)]; [c.573delT (p.S192Afs*65)].

Since then, the patient has undergone regular follow up evaluations, including MR once a year.

At the age of 26 years the MR evidenced normal liver size (longitudinal diameter (LD) 15 cm, volume 1300 cc) and a 9 mm focal lesion on VI segment, T1wi hypointense.

During subsequent evaluations, non-enhanced MR (Magnetom simens avanto 1.5T) has shown slight progressive increase of liver size, while the lesion on VI segment has been stable for approximately 4 years. At the age of 30 years, an increase of the focal lesion to 24 mm was appreciated and, at the same time, four similar smaller lesions appeared; the liver LD was 16.3 cm, with 1600 cc of volume (normal for patient's weight). Lesions showed basal hypointensity in T1wi, moderate T2wi hyperintensity and restriction in diffusion weighted imaging (DWI). After contrast media administration (0.1mmol/kg Gd-BOPTA) all lesions showed intense arterial wash-in, T1 isointensity in portal phase, turning hypointense in late phase, and hypointense during the hepatospecific phase (Fig. 1).

At that time, the clinical examination of the patient was unremarkable, no particular symptom was reported, except for increased fatigue. Echocardiography, electrocardiogram, pulmonary function tests and high resolution CT of the chest were within the normal parameters. Blood tests evidenced mild anemia (Hb 11.5 g/dl), normal platelet count, normal liver function, low HDL (37 mg/dl, n.v. 45-65) with normal tryglicerides. Alpha-fetoprotein and serology for HBV and HCV hepatitis were negative. Levels of plasma biomarkers of macrophage activation and lipid storage remained invariable compared to the previous ones: chitotriosidase 397.3 – 380.0 nmol/ml/h (n.v. 95.8 ± 34.4); oxysterols: cholestane 3β5α6β-triol 50.9 - 63.8 ng/ml (n.v. < 34.8 ng/ml); 7ketocholesterol 135.3 - 131.4 ng/ml (n.v. <92.2 ng/ml).

Considering hepatic imaging findings and the rapid increase of the lesions, HCC was suspected and percutaneous ultrasound guided biopsy was performed, targeted to the main lesion in VI segment (tru-cut needle 18Gx17mm).

On preliminary liver ultrasound B-mode and contrast enhanced ultrasound (CEUS) (using SonoVue 2.2mL IV), the main lesion appeared as an oval subcapsular lesion, moderately hyperechogenic, with minimal acoustic posterior enhancement; on contrast imaging rapid wash-in and steady isoecogenicity, without appreciable wash-out at 80 seconds, was observed (Fig. 2).

Histological methods: the analysis was performed by fixation in neutral buffered formalin and paraffin embedding, with slides 4 micron thick, stained by Haematoxylin and Eosin. The slides underwent usual immunohistochemical procedures with antibodies against liver cells (antihepatocyte antibodies; Hepatocyte OCH1ES, Cell Marque, prediluted) and against macrophages (CD68; KP1 Ventana-Roche, prediluted). Immunostaining was automated using the Autostainer Link 48 by Dakocytomation. No antigen retrieval system was used.

Periodic acid Schiff's method was used to evaluate liver cells glycogen content as follows: the slides were deparaffinized and hydrated to water, than oxidized in 0.5% periodic acid solution for 5, rinsed in distilled water.After 15' in schiff reagent, the slides were counterstained in Mayer's Haematoxylin, dehydrated and mounted (Glycogen stained in red purple).

Histological findings: The major nodule revealed accumulation of foamy cells with inflammatory response and liver cells with clear cytoplasm, due to lipid deposition. Marked Kupffer cells activation with clear cytoplasm was also evident. No atypical or neoplastic cells were present (Fig. 3, 4). The absence of serious fibrosis and of neoplastic features with marked foamy macrophages presence, prompted the diagnosis of a benign nodule due to foamy cells aggregation.

3. Discussion

ASMD is characterized by the lysosomal accumulation of sphingolipids, mainly in macrophages of different peripheral organ and tissues. In the liver, the lipid storage can cause a severe disease, leading in some cases to cirrhosis and hepatic failure [15]. Indeed, liver pathology is considered the second most common cause of death in ASMD patients, after respiratory disease [4]. Nevertheless, as far as we know, an association between ASMD and HCC has not been described, although Cassiman D. et al. reported 2 cases of liver cancer without specifying the subtype [16].

Herein we report the clinical case of a splenectomized ASMD patient in whom annual imaging follow up of the liver showed the development of atypical focal hepatic lesions, without fibrosis or biochemical signs of liver dysfunction. Main characteristics on MR (arterial hypervascularity,

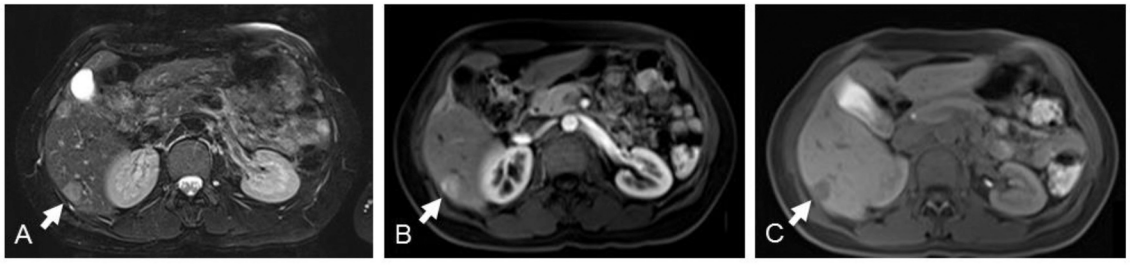

Fig. 1. Liver Magnetic Resonance Imaging showing focal hepatic lesions.
1A: liver TW2WI SPAIR (fat suppression) shows two oval subcapsular nodules of 15mm and 24mm (arrow), intensity is higher than surrounding parenchima, but lower than gallbladder suggesting a non-liquid lesion
1B: largest nodule dynamic 3d imaging T1WI VIBE fat suppression on arterial phase shows intense enhancement (arrow)
1C: largest nodule on hepatospecific phase one hour after contrast injection (Gd-BOPTA) appears hypointense (arrows)

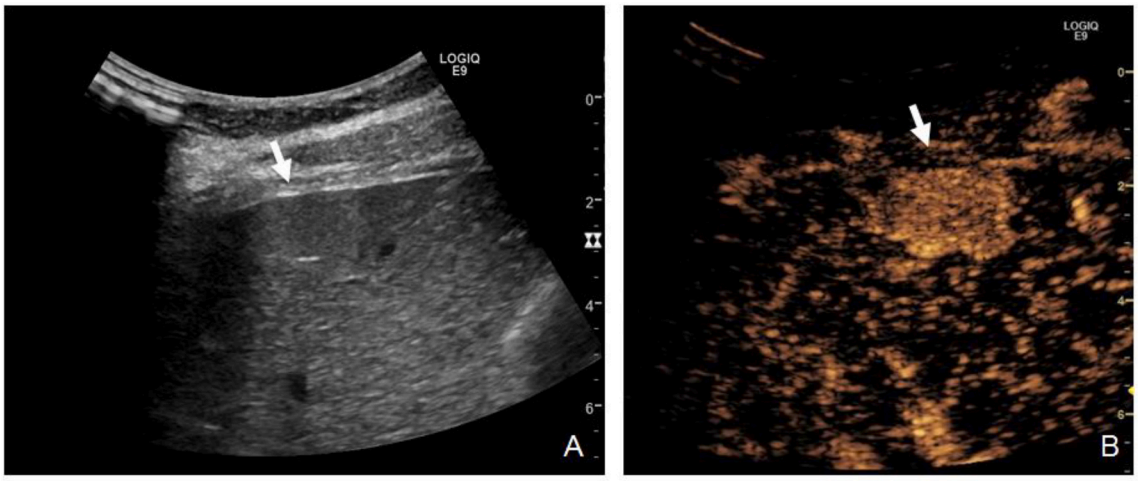

Fig. 2. Contrast enhanced ultrasound (CEUS) of the main focal hepatic lesion.
2A: liver US B-mode examination shows a VI segment subcapsular 24mm iso-hyperechogenic nodule (arrow)
2B: CEUS same nodule shows arterial hyperintensity at 12 seconds from injection (arrow)

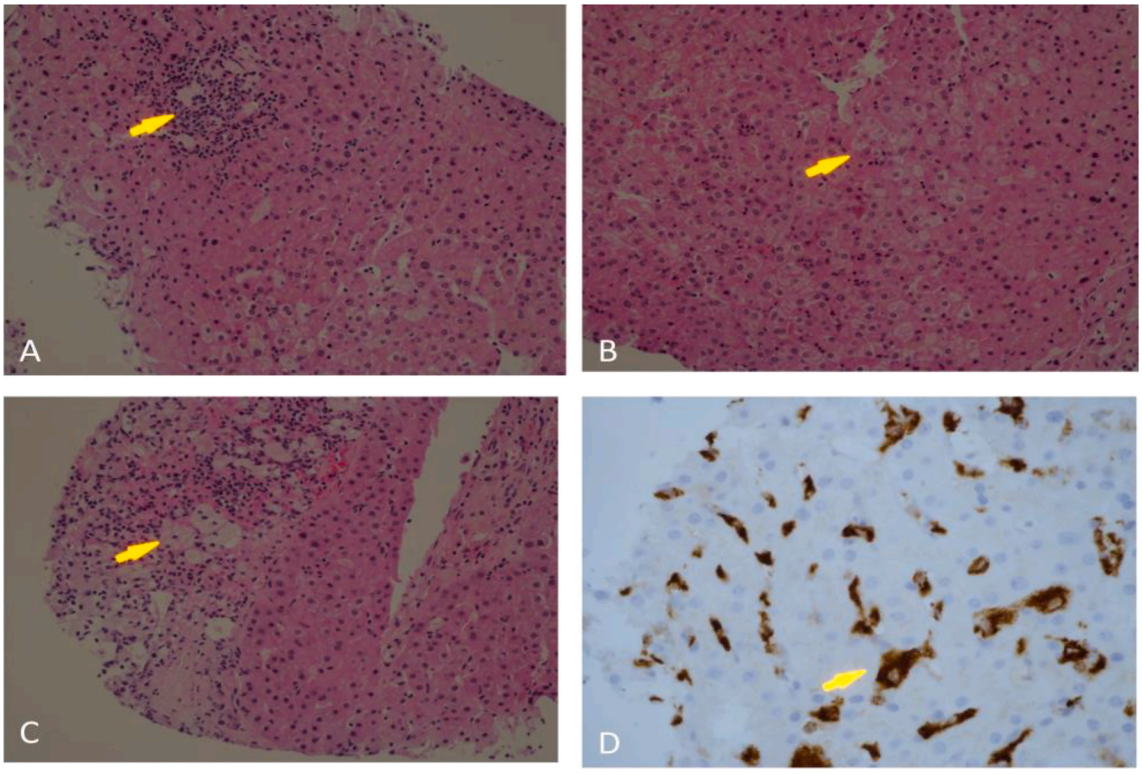

Fig. 3. Histological appearance of foamy macrophages collection and lipid deposition in liver cells.
3A: Foamy macrophages within liver parenchyma, with inflammatory response. H&E 10X (arrow)
3B: Sparse foamy macrophages in a portal tract H&E 10X (arrow points to an area containing some foamy cells)
3C: Cytoplasmic liver cells lipid deposition (clear cells) H&E 10X(arrow)
3D: CD68 (KP-1) reactive macrophages (foamy cells) and activated Kupffer cells 20X (arrow points to a large foamy cell)

hepato-specific phase hypointensity and restriction on DWI) were compatible with hypercellular focal lesions of non-hepatocytic, undifferentiate hepatic or dysfunctional composition. Therefore, radiologically, differential diagnosis was among malignant primitive lesions of the liver (HCC), secondary lesions (hypervascular metastasis), and benign lesions (hemangioma, adenoma, focal nodular hyperplasia or, in this case, deposit nodules) [17,18]. The rapid enlargement of the main lesion prompted us to perform a biopsy to investigate its nature and to exclude the presence of an aggressive/malignant lesion. The analysis of the biopsy material confirmed that it was a deposit nodule, showing accumulation of clear cells with granular cytoplasm, with inflammatory response.

In Gaucher disease, considered the most common lysosomal storage disorder, deposit nodules in the liver and spleen, called Gaucheromas are widely described [19,20]. Conversely, to our knowledge, only a single case of focal hepatic lesions representative of storage nodules in ASMD was previously reported, confirming our findings, although it was evaluated with a much older technology (no MRI, no CEUS) [21]. Thus,

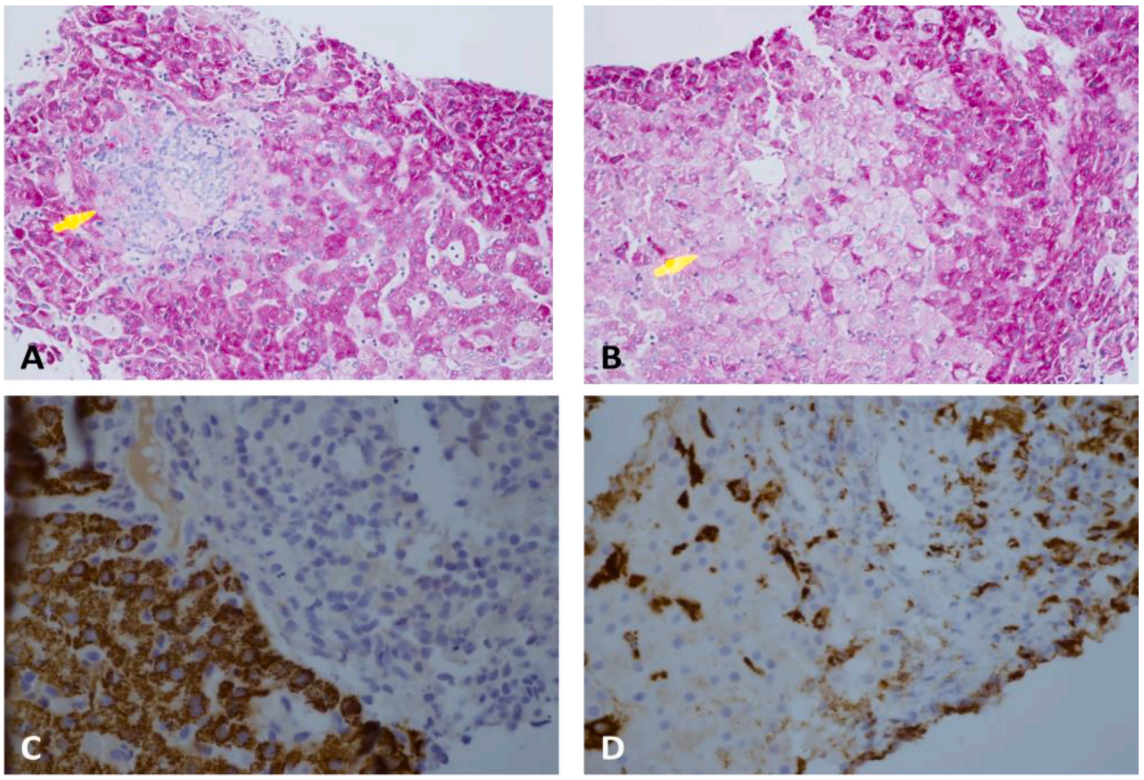

Fig. 4. Lipid deposits in macrophages and liver cells explaining the origin of the focal hepatic lesion
4A: Foamy macrophages PAS negative (absence of glycogen) 10X (clear area on the left)
4B: Liver cells PAS negative due to lipid deposition with glycogen reduction or absence 10X
4C: Antihepatocyte antibody: unreactive macrophages 20X (right side)
4D: Foamy macrophages CD68 (KP-1) reactive (upper right) 20X

this is the first report of a focal lesion, representative of foamy cells accumulation, well characterized in a patient affected by ASMD.

The mechanism involved in foamy macrophages aggregates formation should be further investigated, but we can hypothesize, similarly to what happens for Gaucheromas, a role of the chronic immune system activation. Indeed, in patients who have developed Gaucheromas an increased production of chemoattractive molecules, including tumor derived chemotactic factor (CCL2) and cytokines such as vascular endothelial grow factor (VEGF), has been described. This pro-inflammatory status recruits monocyte fractions in the site where Gaucher cells accumulate, leading to a snowball effect and formation of the pseudo-tumor Gaucheroma mass [12].

In Gaucher disease the formation of Gaucheromas has been correlated with more severe disease and with previous splenectomy [20]. Our patient had a mild ASMD disease burden (no lung involvement, normal tryglicerides), however, she was splenectomized. Nowadays, splenectomy is not recommended in ASMD and Gaucher disease anymore, since it does not cure the disease and can increase lipid accumulation in other organs such as the liver, the respiratory system and the bone [22,23]. However, it is possible to hypothesize that in our patient the spleen removal have triggered the formation of deposit nodules in the liver.

Concerning disease treatment, the enzyme replacement therapy (ERT), available for Gaucher disease for more than 20 years, seems to be unable to reduce the size of preexisting Gaucheromas, despite the effect on the reduction of liver volume [24]. This data suggests that these focal lesions are areas in which the enzyme is less effective. Furthermore, the development of a Gaucheroma in a pediatric patient who had been on ERT for 2 years has been reported [25]; therefore it is unclear whether ERT could prevent Gaucheromas's formations.

As regards ASMD, a new specific enzyme replacement therapy with recombinant ASM (rhASM) is now under investigation (phase III). Preliminary data on its effect on the liver are encouraging, showing progressive clearance of sphingomyelin storage in liver biopses over 42 months of treatment [26,27]. Focal foamy cells accumulation was not reported in any of the treated patients described so far [26–28].

Interestingly, rhASM is also under investigation as a potential therapeutic agent for HCC in the general population [29]. Indeed, altered sphingolipid metabolism and particularly a reduction of ceramide levels are common features in cancer development. Thus, rhASM by promoting the conversion of sphingomyelin in ceramide, would increase ceramide levels, potentially enhancing ceramide-mediated death of tumor cells [30]. Based on these theories, rhASM could potentially exert an additional beneficial effect in preventing malignancies in ASMD patients, but further long term treatment studies are needed to verify this hypothesis.

On the radiological point of view, imaging findings in the patient reported here, are similar to those commonly found in hepatic Gaucheromas, displaying MRI hyperintensity on T2wi and hypointensity in T1wi, enhancing lesions after contrast media. However, imaging characteristics of Gaucheromas are variable, probably reflecting variations in the composition of the lesion (eg. degree of fibrosis), and are not always easy to differentiate from a neoplasm such as HCC. As this variability and uncertain radiological appearance includes malignant lesions in the differential diagnosis, strict imaging follow-up and/or biopsy is important. The diagnosis of Gaucheromas remains a diagnosis of exclusion [20,31]. In a study examining a large cohort of Gaucher patients who underwent liver imaging follow-up, 25% presented liver focal lesions, 16% of whom were finally diagnosed as HCC [20]. Malignancy is therefore something to be aware during follow up of patients with liver storage diseases. Regemboog et al. have proposed a follow up algorithm for focal hepatic lesions in Gaucher disease, which recommends more attention in patients with previous splenectomy and lesion's dimensions greater than 1 cm. Although data on long term follow up of

adult patients with ASMD are still scarce, liver malignancy has been described in two case reports [16], so it can represent a complication of the disease.

In the patient reported here, the enlargement of a known focal hepatic lesion, and the development of new lesions presenting contrast enhancement typical for HCC, prompted us to perform an ultrasound guided percutaneous biopsy to clarify the diagnosis.

Indeed, although our case demonstrates the possible rapid formation of benign liver storage nodules in ASMD, liver nodules increasing in number and size should always been further analyzed by second imaging modality and eventually biopsied if diagnostic uncertainty persists.

4. Conclusions

Focal liver lesions can be evidenced during the imaging follow-up of patients affected by ASMD. Benign storage nodules should be considered in the differential diagnosis.

Further imaging studies including more patients are needed to assess prevalence, characteristics and evolution of focal hepatic lesions in ASMD.

Authors contributions

AS evaluated and followed the patient at the RCCRD, wrote the case report and drafted the manuscript; AV and AP performed the radiological examinations and wrote the parts of the paper concerning imaging; CA performed the histological analysis and wrote the parts of the paper concerning histology; AD performed the biochemical and genetic diagnosis of ASMD and revised the final draft; MS contributed to the final article revision; BB critically revised the paper.

Declaration of Competing Interest

None

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