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Glycogen storage disease type III-hepatocellular carcinoma a long-term complication?

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Abstract

Background/Aims—Glycogen storage disease III (GSD III) is caused by a deficiency of glycogen-debranching enzyme which causes an incomplete glycogenolysis resulting in glycogen accumulation with abnormal structure (short outer chains resembling limit dextrin) in liver and muscle. Hepatic involvement is considered mild, self-limiting and improves with age. With increased survival, a few cases of liver cirrhosis and hepatocellular carcinoma (HCC) have been reported.

Methods—A systematic review of 45 cases of GSD III at our center (20 months to 67 years of age) was reviewed for HCC, 2 patients were identified. A literature review of HCC in GSD III was performed and findings compared to our patients.

Conclusions—GSD III patients are at risk for developing HCC. Cirrhosis was present in all cases and appears to be responsible for HCC transformation There are no reliable biomarkers to monitor for HCC in GSD III. Systematic evaluation of liver disease needs be continued in all patients, despite lack of symptoms. Development of guidelines to allow for systematic review and microarray studies are needed to better delineate the etiology of the hepatocellular carcinoma in patients with GSD III.

Keywords

Hepatocellular carcinoma; Glycogen storage disease type III; Liver cirrhosis; Debranching enzyme deficiency; Cori disease; Hepatomegaly; Hypoglycemia

1. Introduction

Glycogen storage disease III (GSD III), also known as debrancher enzyme deficiency or Cori disease (OMIM # 232400), is an autosomal recessive disorder that results from deficiency of glycogen-debranching enzyme (amylo-1,6 Glucosidase; EC 3.2.1.33 and 1,4-α-D-glucan 4-α-D-glycosyltransferase; EC 2.4.1.25). Deficiency results in an incomplete glycogenolysis and accumulation of glycogen with abnormally short outer chains (resembling limit dextrin) in the liver and muscle [1]. There are two major GSD III subtypes; GSD IIIa the most common subtype, accounting for ~80% of the cases where patients have both liver and muscle involvement and IIIb accounting for approximately 15% of all GSD III where patients have enzyme activity lacking only in liver. Symptoms common to both subtypes are hepatomegaly, hypoglycemia, short stature, and dyslipidemia [2]. Only patients with type IIIa have a myopathy and cardiomyopathy [2].

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Treatment for GSD III is primarily dietary and is aimed at maintaining euglycemia. This is achieved by frequent meals high in carbohydrates and cornstarch supplements alone or with gastric tube feedings. For patients with myopathy, in addition to management of hypoglycemia, a high protein diet is recommended [1]. Patients in good metabolic control show improvement in growth, development, and metabolic parameters such as levels of cholesterol and triglycerides [1].

The liver is affected in a variety of ways in GSD III. Hepatomegaly is noted in childhood and liver enzymes (ALT, AST) are typically elevated, providing evidence of hepatocellular damage. Liver histology shows distension of hepatocytes by glycogen accumulation, and presence of periportal septal fibrosis, early in the disease process, perhaps related to the accumulation of abnormally short-branched glycogen [3]. Hepatic involvement in GSD III is considered mild and almost always self-limiting. Liver symptoms typically improve with age and the major cause of morbidity is the muscle disease where symptoms usually manifest in the second decade of life. Although liver disease is reported as improving with age there are reports of liver adenomas and a few publications of liver cirrhosis, with some progressing to liver failure [4,5]. To date four isolated cases of hepatocellular carcinoma (HCC) in GSD III have been reported [6–9].

As life expectancy of patients with GSD III improves, long-term liver complications continue to be reported. We report our experience of HCC in 2 patients with GSD III in a cohort of 45 patients followed in the Metabolic Clinic at Duke University Medical Center from 1958 to 2006, which serves as a national GSD referral center. In this manuscript we review the literature and add our experience. This is the first systematic review of HCC in this population.

2. Materials and methods

Following Institutional Review Board approval a chart review of 45 patients with GSD III (21 females, 24 males) with a median age of 13.7 years (range 20 months–67 years) at the time of analysis was conducted for HCC frequency. A diagnosis of GSD III was made based on increased glycogen content, an altered ratio of glucose-1-phosphate/glucose and evidence of debrancher enzyme deficiency in liver and/ or muscle biopsy.

As part of their clinical workup all patients receive a comprehensive physical evaluation, dietary evaluation with an experienced metabolic dietitian and laboratory evaluations, including a hepatic profile, lipid panel, creatine kinase (CK), alphafetoprotein (AFP), and carcinoembryonic antigen (CEA). In addition, patients have regular liver imaging studies consisting of an ultrasound examination, MR examination or CT scan to evaluate liver size, presence of liver adenomas, and liver architecture for evidence of cirrhosis.

All imaging examinations for the two patients identified with HCC were reviewed by a single subspeciality certified radiologist with 15 years of experience (D.F.). Examinations were reviewed and compared with original dictated radiology reports. There were no disagreements between image review for this investigation and the original report. Images were reviewed on either hardcopy (film) or softcopy (PACS) workstation.

Imaging modalities consisted of CT, MR, and ultrasonography. Because of the extended period of observation, a variety of modalities, and techniques were used. For example, CT examinations were performed on either single detector or multi-detector helical scanners. At our institution, contrast-enhanced CT examinations are nearly invariably performed for liver assessment. All MR imaging was with a 1.5 Tesla system consisting of a minimum of T1- and T2-weighted images. Sonographic examinations were performed at our institution and consisted of a standard examination utilizing 2.5–5.0 MHz transducer, depending on the size of the patient. Images were obtained in standard planes representing a sagittal and axial survey

of the liver. The presence or absence of hypoechoic lesions was noted and lesions, when present, were measured using electronic calipers. A survey of hepatic size consisting of measurements in the mid and anterior axillary and mid clavicular sagittal locations was used to assess for interval change in liver extent, although liver volume was not able to be determined from these measurements. All pathologic specimens were reviewed by one board certified pathologist with more than 20 years of specialty experience in gastrointestinal and liver pathology (MG).

Genomic mutation analysis was done on DNA isolated from whole blood using Pure Gene DNA isolation kit (Gentra systems) and mutations were studied in detail through genomic DNA sequencing. Primer sequences and conditions used for PCR amplification of each exon of the GDE gene have been published earlier [10–13]. Sequencing was performed using dRhodamine dye terminator Cycle sequencing reaction kit on an ABI Prism 377 or 310 DNA sequencer (PE Applied Biosystems, Foster City, CA).

3. Case reports

3.1. Patient 1

At age 12 months this Caucasian male presented with hepatomegaly and delayed motor milestones, and was clinically diagnosed with GSD type III. When first seen at Duke (age 35 years), he complained of hypoglycemia symptoms that resolved with eating. The patient had a cardiomyopathy and left ventricular hypertrophy with normal cardiac function. He also reported a generalized muscle weakness. A diagnosis of GSD IIIa was confirmed enzymatically by documenting DE deficiency in both liver and muscle tissues, done at the GSD diagnostic laboratory at our institution. DNA sequencing of the GDE gene revealed this patient to be a compound heterozygote for Gly655Arg (missense mutation in exon 16) and *IVS 29-17 T > A* (an intronic splicing mutation; possibly resulting in activation of a cryptic splice site) mutations, that have not been reported before in any other GSD III patients. Fifty-four normal human DNA samples sequenced for GDE did not harbor these changes. Cornstarch and a high protein, complex carbohydrate diet were recommended, however he was noncompliant. By age 43 he was wheelchair bound.

During multiple evaluations from the ages of 47–53 his liver function studies (AST, ALT, alkaline phosphatase, bilirubin) remained stable and within normal limits with the exception of a mildly elevated AST, and alkaline phosphatase (1–2 times the upper limit of normal). At age 54, mild increases in total bilirubin 1.9 (reference range 0.2–1.2 mg/dL), AST 182 (normal limits, 10–60 U/L), ALT 109 (normal limits, 10–60 U/L), and alkaline phosphatase 354 (normal limit, 30–135 U/L) were noted. Two months later he reported a progressive shortness of breath. He was noted to have jaundice, ascites, pleural effusions, and hepatomegaly. An abdominal CT scan showed a large right liver mass and multiple satellite lesions (Fig. 1). Abdominal MR imaging demonstrated multiple hepatic lesions, with probable tumor thrombus occluding the portal vein and liver cirrhosis. At that time, liver parameters were elevated with a total bilirubin of 6.6, AST of 410, ALT of 115, alkaline phosphatase of 509 and AFP was 51 ng/mL (normal 10–15). A fine needle aspiration cytology with cell block revealed HCC (Fig. 2). Due to the advanced stage of the liver tumor it was felt that the patient would not benefit from further therapy and he died shortly thereafter.

3.2. Patient 2

This 67-year-old Caucasian male presented with hepatomegaly, and a history of seizures and hypoglycemia as an infant. He was diagnosed with GSD III at age 5 years by a liver biopsy. A diagnosis of GSD IIIa was confirmed by demonstrating deficient debranching enzyme activity in both liver and muscle samples at age 32. He has been followed at our clinic for over

30 years. He was treated with frequent meals, rich in complex carbohydrates and also a high protein diet. He showed improvement in growth and no hypoglycemic episodes since childhood. He required no cornstarch supplementation. The patient showed progressive muscle weakness and was wheelchair bound by age 52. His liver enzymes had been within the normal ranges with the exception of a mildly elevated ALT (two times above baseline on one occasion). Liver ultrasound at age 36 and again at age 39 were reported as normal with only diffusely increased echogenicity likely due to glycogen deposition. Follow-up examination at age 54 demonstrated a single 2 cm nodule, felt to be an adenoma in the left lobe medial segment of the liver. Two years later the initial nodule remained stable; however a new 9 mm nodule was noted in the same lobe. Four years later a liver ultrasound showed a slight increase in size of both of the lesions, but these remained stable in a follow-up CT scan performed at age 62 years (Fig. 3A) and by ultrasound at the age of 63. Because these two lesions were followed for 7–9 years, they were classified as benign liver lesions, most likely adenomas. AFP was within normal limits at the ages of 62 and 63. The patient was lost to follow-up until age 67. Clinically, he was unchanged except for progressive muscle weakness. Laboratory work drawn at that visit demonstrated normal AST, ALT, alkaline phosphatase, and total bilirubin. The patient declined imaging studies due to difficulty in tolerating the scanning procedures. GDE gene sequencing showed this patient to be a compound heterozygote for two novel mutations; a 12 bp deletion resulting in loss of 4 aa (Val491-Arg494) in exon 12 and an intronic mutation (*IVS* 31 + 5 G > A) possibly resulting in activation of a cryptic splice site. The patient presented a month later with a right hemiparesis. Brain MRI showed a hemorrhagic mass in the left occipital lobe that was felt to represent a metastatic deposit. Subsequent abdominal imaging showed multiple nodules throughout the lungs and multiple ill-defined low-attenuation lesions in the hepatic parenchyma, an enlarged left adrenal nodule, and several areas of abdominal adenopathy with a concern of metastases or HCC (Fig. 3B and C). A CT guided liver needle biopsy did not show tumor cells but demonstrated cirrhosis. Adrenal tissue and brain tumor biopsies were consistent with metastatic HCC based on immunohistochemical studies and tumor morphology (Fig. 4 and Fig 5). Despite radiation therapy, the patient died shortly thereafter.

4. Discussion

Childhood hepatomegaly and liver symptoms in GSD III are usually considered self-limited with no symptoms of hypoglycemia or active liver disease typically after the second decade of life. The major cause of morbidity is progressive myopathy for patients with GSD IIIa. There are some gentotype/phenotype correlations in regard to clinical severity in patients with GSD IIIa. To date, three common mutations have been identified in Caucasian patients with GSD-IIIa (R864X, R1228X, and W680X accounting for ~28% of the known mutations). Our two patients did not have these mutations, or other severe intronic splicing or exonic (nucleotide deletion/addition) frame shift or nonsense disease causing mutations reported in the literature so far. It cannot be ascertained with certainty that severe myopathy caused in our patients is because of the novel mutations seen in these two patients. More patients with a severe phenotype of GSD III need to be screened for better genotype/phenotype correlations in GSD type IIIa [12].

Liver fibrosis is seen early in the disease process, however hepatic involvement is considered mild and self-limiting. Serum AST and ALT are markedly elevated in the first decade of life, but tend to decrease significantly thereafter [2]. Parameters of liver function such as albumin and prothrombin time are also normal, until the onset of overt cirrhosis which is atypical in the vast majority. There are a few reports of liver cirrhosis and HCC in patients with GSD III [6–9]. Liver cirrhosis is thought to be due to progressive accumulation of glycogen that is abnormal in structure leading to damage to hepatocytes. In our cohort of 45 patients, only two have developed progressive liver cirrhosis. One is a 24-year-old female who developed liver

cirrhosis with portal hypertension at age 22. This patient has a prolonged PT, low serum albumin, a hypercoagulable state, hyper-splenism and portal hypertensive colopathy. The other is a 52-year-old male with GSD IIIb who has developed overt liver cirrhosis with a prolonged PT. Both patients have no adenomas or other risk factors for HCC. Both are currently on a liver transplant list.

Liver adenomas are well-recognized findings in GSD I with a prevalence from 22% to 75% [1]. Adenomas typically present in GSD I by the second or third decade, mostly appearing during or after puberty [1,14]. The pathophysiologic mechanism of adenoma development is unclear, but appears to be related to metabolic rather than hormonal causes [15]. The relationship between good metabolic control and the appearance of adenomas in GSD I patients is unclear, although some reports suggest a lower incidence and even regression of the tumors in adequately treated patients [16,17].

In contrast, adenomas are not as common in patients with GSD III. In a study of 16 GSD III patients (age range 14–24 years) 4 developed adenomas (age range 10–19.5 years) [4]. In our GSD III cohort 2 of the 45 patients (4.4%), followed at Duke for more than 30 years, have developed adenomas, in both instances small and stable, in contrast to the ones noted in GSD I. This includes patient 2 described in this paper. The other is a 35-year-old Caucasian female who has small, stable adenomas. Twenty patients in our cohort are greater than age 20 years. None of our patients younger than age 35 years have developed adenomas to date.

Our two cases with GSD III and HCC add to the four previous reports published in the literature (Table 1). Both patients failed to show significant elevation of transaminases above their typical baseline values at the time of HCC development. Both were diagnosed late in life and illustrate a common issue in managing meta- of stable liver cirrhosis at the time of HCC development. Patient 2 had the presence of small stable adenomas by radiologic assessment at the time of HCC development. It is unclear whether these lesions were adenomas or early stage HCC, however, given the stability in size over several years, the diagnosis of adenomas was favored. AFP and transaminases were normal in this patient. Patient 1 did not have adenomas at the time of HCC development and had a mildly elevated AFP at the time of advanced metastatic HCC. Transaminases and AFP therefore do not appear to be reliable markers of liver disease or HCC transformation in these patients similar to what has been noted in GSD I [16]. Other reports of patients with GSD III and HCC mention that all had mildly to grossly elevated AFP levels at the time of HCC diagnosis; however, AFP levels prior to diagnosis were not reported (Table 1).

HCC is the 5th most common malignancy worldwide because of the increasing incidence of hepatitis B and C [18]. HCC is primarily a disease of older individuals (>65 years of age) and men are more likely than women to develop HCC. Risk factors include hepatitis B and C infection, chronic alcohol consumption, diabetes, steatosis and obesity [19]. These risk factors were not noted in either of our patients.

The mechanism for tumorgenesis in GSD III is unknown but appears different than in GSD I, which is believed to be an adenoma–carcinoma sequence. In GSD III, it may be that liver cirrhosis is facilitating this carcinoma transformation, which is a well-recognized association. The previous four reports as well as our 2 patients with HCC all had liver cirrhosis before the onset of HCC. In our two cases only one had a presumed adenoma by radiologic assessment. While this does not prove that some patients with GSD III and HCC did not develop it from an adenoma–carcinoma mechanism, it questions the validity of this mechanism as the sole etiology of HCC in these patients. At the current time, it thus appears that liver cirrhosis in GSD III is the major contributor to HCC development, similar to what is seen in hepatitis B and alcoholic hepatitis. Researchers have yet to elucidate the etiology of this liver cirrhosis–

carcinoma sequence in the absence of other risk factors in the development of HCC in GSD III. Detailed GDE gene analysis on additional patients with GSD III and HCC might help to define any underlying genotype–phenotype correlations, if any.

As patients with GSD III are surviving longer, new long-term complications are being described. Progressive liver cirrhosis and HCC may be a result of longer survival in these patients. The general characteristics and follow-up profile of the patients in this series are common to many with the disease: late onset of appropriate therapy, irregular follow-up and poor compliance. Some suggest that GSD III patients with advanced liver disease should be considered for liver transplant which might be a viable alternative for patients not showing advanced myopathy [5]. Management guidelines have been developed for GSD type I patients based on expert opinion and the results of the European Study on Glycogen Storage Disease I [20]. Similar guidelines should be developed for monitoring and treatment of patients with GSD III. Complete GDE gene mutation analysis performed on a larger patient population to delineate any genotype–phenotype correlations or liver gene expression microarray studies to explore the liver adenoma/cirrhosis to HCC sequelae needs to be under taken in order to better understand the disease mechanism in GSD type III.

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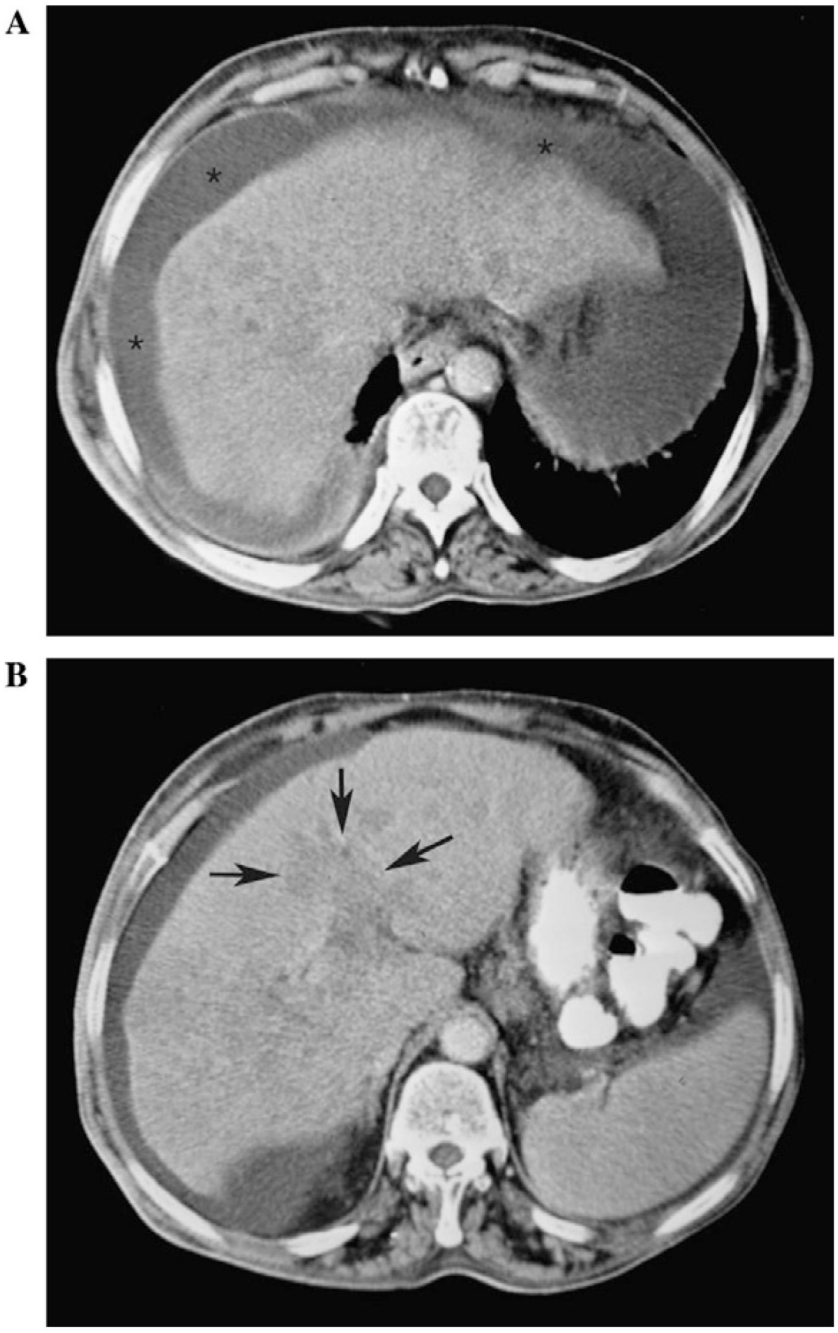

Fig. 1.

Patient 1. (A) A 54-year-old male with GSD type IIIa and hepatocellular carcinoma. (A) IV contrast enhanced CT examination of the upper liver shows heterogeneous parenchyma with multiple low attenuation regions. The liver was not enlarged. Ascites (*) surrounds the liver. (B) Image from a IV contrast enhanced CT examination at the region of the upper porta hepatis again shows scattered low-attenuation lesions with a more focally defined low-attenuation region in the area of the left portal vein (arrows). Ascites is again evident around the liver.

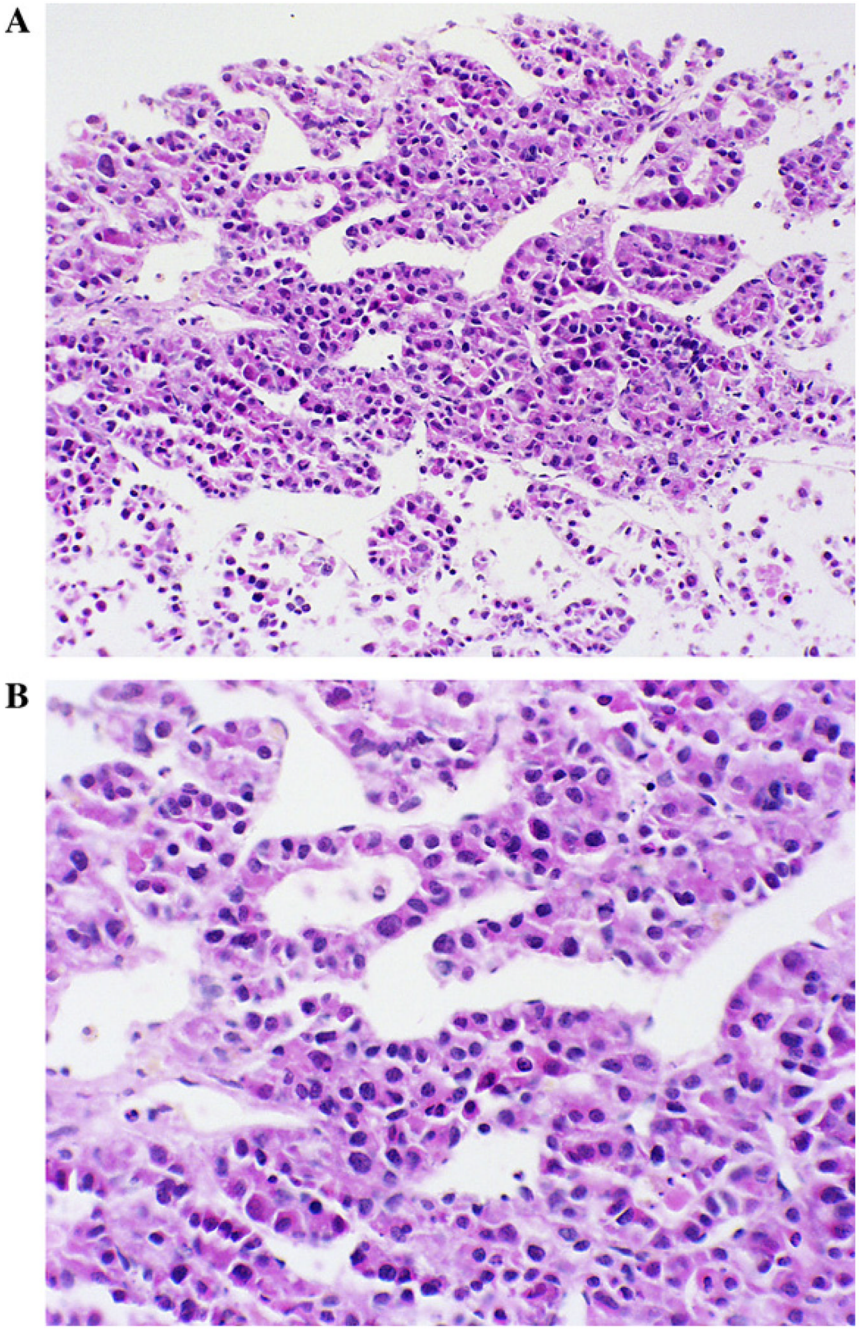

Fig. 2.

Patient 1. A fine needle aspiration cytology of one of the liver lesions (A) reveals a cellular population of tumor cells, some organized in pseudoacinar rosettes and some in trabeculae with poor cohesion and no intervening desmoplastic stroma. This architecture is characteristic of hepatocellular carcinoma in biopsy specimens. A higher power view (B) demonstrates rudimentary hepatocellular features including polygonal cells with granular eosinophilic cytoplasm and central nuclei, but with the high nuclear cytoplasmic ratio and mild nuclear irregularity of moderately well-differentiated hepatocellular carcinoma. (Fig. 1A 20× and B 40×). [This figure appears in colour on the web.]

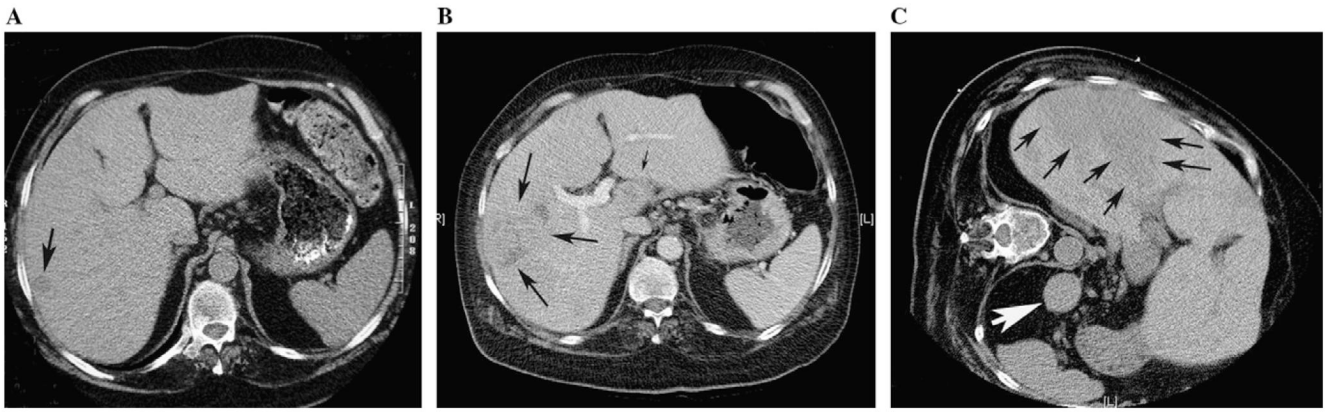

Fig. 3.

Sixty-two year-old male (A) axial image of the upper abdomen from a non-contrast enhanced CT examination shows a low-attenuation lesion in the right lobe of the liver (the second lesion is not shown) (arrow). (B) IV contrast-enhanced axial CT image at the level of the portal vein performed at age 67 years shows a large, poorly defined heterogeneous mass in the same region (large arrows). A smaller area seen adjacent to the caudate lobe (small arrow) represents metastatic adenopathy. (C) Axial image from a non-contrast enhanced CT examination obtained in the left lateral decubital position at a level just inferior to that in (B) shows the low attenuation lesion in the right lobe of the liver (arrows). Fine needle aspiration of the liver was not diagnostic for malignancy. Biopsy of the adrenal lesion (large arrow) was positive for hepatocellular carcinoma.

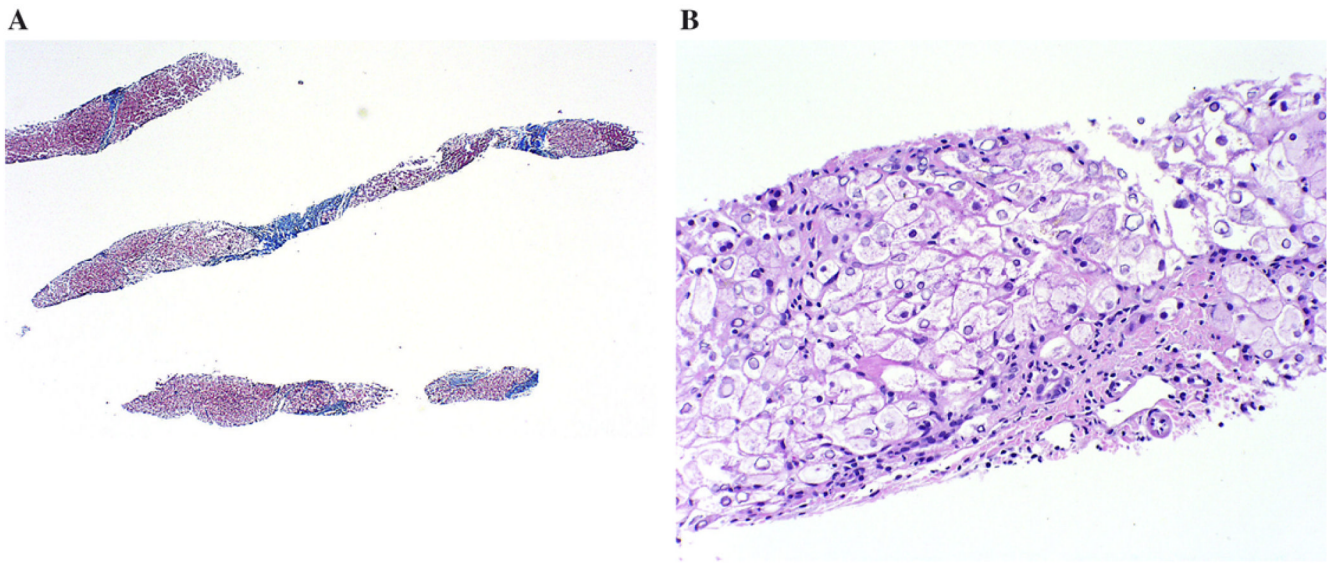

Fig. 4.

Patient 2. A CT-guided biopsy of the liver reveals cirrhosis (A). Trichrome stain reveals fibrous septa surrounding regenerative nodules of hepatocytes. Hepatocytes are expanded by glycogen in the H&E stain (B) (Fig. 2A 2× and B 20×). [This figure appears in colour on the web.]

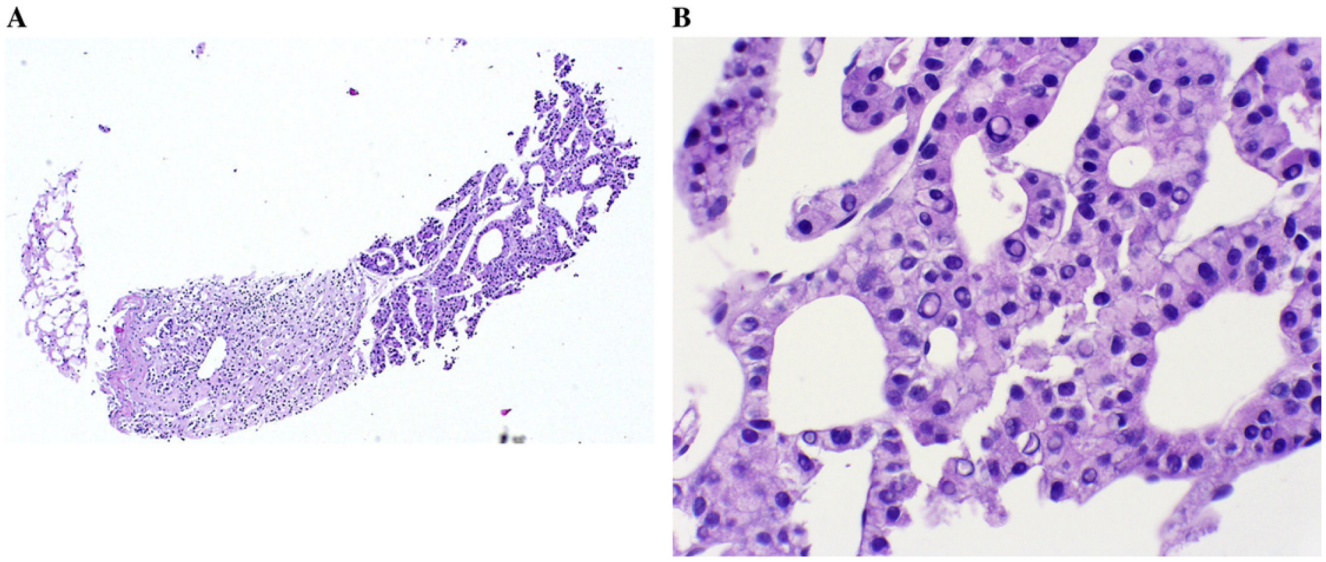

Fig. 5.

Patient 2. CT-guided biopsy of the adrenal mass confirms the diagnosis of metastatic well-differentiated hepatocellular carcinoma involving the adrenal gland (A) single line, adrenal and fat; double line, hepatocellular carcinoma. Similar to the carcinoma in patient 1, poorly cohesive trabeculae and pseudoacini of tumor cells are seen with granular cytoplasm, high nuclear-to-cytoplasmic ratio and mild nuclear irregularity (B) (Fig. 3A 4× and B 40×). [This figure appears in colour on the web.]

Table 1

Reports of hepatocellular carcinoma in patients with glycogen storage disease type III

Patient	Age at HCC diagnosis, gender/ethnicity	AFP level at time of HCC diagnosis (0–15 ng/mL)	Presence of liver adenomas/cirrhosis
Cosme et al.	31 years F/Hispanic	155,790	Progressive liver cirrhosis
Siciliano et al.	56 years F/Caucasian	600	Progressive liver cirrhosis – Hepatitis B and C negative
Haagsma et al.	32 years F/Caucasian	18	Advanced liver cirrhosis – Hepatitis B and C negative
Shimizu et al.	32 years F/Japanese	Increased (details unavailable)	Liver cirrhosis
Patient 1	54 years M/Caucasian	51	Stable liver cirrhosis – Hepatitis B and C negative
Patient 2	67 years M/Caucasian	Normal	Stable liver cirrhosis – Hepatitis B and C negative, presence of small stable adenomas