Spontaneous Regression of Hepatic Adenoma in a Patient with Glycogen Storage Disease Type I after Hemodialysis: Ultrasonographic and CT Findings

Hiroko Iijima#, Yuji Moriwaki, Tetsuya Yamamoto, Sumio Takahashi, Takashi Nishigami* and Toshikazu Hada

Abstract

A 23-year-old woman was admitted to our hospital with recurrent gouty arthritis. Laboratory findings showed hypoglycemia, lactic acidosis, hyperlipidemia, and hyperuricemia, with normal values of serum alfa-fetoprotein (AFP) and protein induced by vitamin K absence (PIVKA-II). A diagnosis of glycogen storage disease type I (GSD-type I) was made on the basis of the laboratory data, liver biopsy findings, and partially deficient thrombocyte glucose-6-phosphatase (G-6-Pase) activity. Ultrasonography and computed tomography revealed multiple focal hepatic masses. Biopsied specimens of the lesion demonstrated a hepatic adenoma, which changed in appearance in the relatively short period between echography and computed tomography. This interesting phenomenon may highlight the importance for careful follow-up of hepatic adenomas, because of the potential of rupture, hemorrhage, or malignant transformation. During follow-up, the present patient received hemodialysis due to renal failure, and the adenoma regressed spontaneously after 8 years. Included are diagnostic images, demonstrating the association of hepatic adenoma and GSD-type I.

Key words: von Gierke’s disease, hepatic tumor, natural regression, diagnostic imaging

Introduction

Glycogen storage disease type I (GSD-type I) (glucose-6-phosphatase deficiency) is a metabolic disorder of autosomal recessive inheritance characterized by hypoglycemia, hepatomegaly, and growth retardation. Many patients with this disease suffer from severe acidosis or hypoglycemia in their childhood. However, recent advances in nutritional support preventing nocturnal hypoglycemia have obtained longer survival times for GSD-type I patients to adolescence and even adulthood. As a result, in older patients, other complications such as gout, hyperlipidemia, and hepatic tumors are frequently observed. Previously, hepatic adenoma was considered to be a rare complication of GSD-type I, but has recently been recognized more frequently with the development of diagnostic techniques.

We encountered a case of GSD-type I complicated with a hepatic adenoma, which changed its appearance in a relatively short period of time between ultrasonography and computed tomography, and then naturally regressed after 8 years, during which time the patient received hemodialysis.

Case Report

A 23-year-old woman was referred to our gout clinic in October 1990 for the management of recurrent gouty arthritis. She had a 10-year history of gout, which had been resistant to medical therapy. The patient was a first child of unrelated parents and her birth was uneventful. There was no particular family history of note. She has not used oral contraceptives. A physical examination showed that the patient was apparently in good health. She was 167 cm tall and weighed 69 kg with normal vital signs. The abdomen was soft and nontender, however, her liver could be palpated 3 cm below the right costal margin at the mid-clavicular line. Neither kidney was palpable. Swelling and redness of the metatarsophalangeal (MTP) joint of the right great toe was also noted. Other clinical examinations were normal. Her red blood cell count was 305\times10^{12}/\text{mm}^3, hemoglobin level 8.9 g/dl, platelet count 65.5\times10^{12}/\text{mm}^3, and white blood cell count 10,500/\text{mm}^3 with a normal differential. Blood chemistry showed the following values: Fasting blood sugar, 53 mg/dl; serum uric acid, 13.1 mg/dl; serum creatinine, 0.64 mg/dl; urea nitrogen, 12.0 mg/dl; total cholesterol, 281 mg/dl; triglyceride, 392 mg/dl; and lactic acid, 73.0 mg/dl (normal 3.3–
Plasma glucagon level was 120 pg/ml (normal <150 pg/ml). The serum values of alfa-fetoprotein (AFP) and protein induced by vitamin K absence (PIVKA-II) were within the normal range. Urinalysis was positive for protein. The diagnosis of GSD-type I was confirmed by a screening method (glucose and galactose tolerance tests), a glucagon tolerance test, and an assay of G-6-Pase activity in thrombocytes. Responses to glucose, galactose, and glucagon tolerance tests were hyperglycemia (diabetic pattern), hypoglycemia, and normoglycemia (no response), respectively. G-6-Pase activity in thrombocytes was 0.24 U (normal 0.90±0.19 U, n=3). An abdominal ultrasonography performed on December 14, 1990 revealed moderate hepatomegaly with increased hepatic echogenecity and deep attenuation, which was probably caused by glycogen accumulation and fatty metamorphosis. Further, the ultrasonography demonstrated multiple focal hepatic masses in both lobes (Fig. 1), the largest of which was a hypoechoic left liver lobe lesion measuring 12x16 mm (Fig. 2 upper). Most of the multiple small nodular lesions were also hypoechoic. A computed tomography (CT) taken on December 3, 1990 disclosed moderate enlargement of the liver, with a high density area of 1.5 cm (Fig. 3, upper) corresponding to the largest mass seen on the ultrasonogram. An infusion hepatic angiography performed on December 13, 1990 demonstrated hypervascular masses and tumor stain nodules throughout the liver in the late capillary and venous phases. Specimens biopsied from the liver (December 19, 1990), except for the nodular lesions, disclosed liver cells crowded with glycogen, but the nature of the specimen biopsied from the largest mass could not be diagnosed. The patient was followed by ultrasonographic and CT examinations; her findings remained unchanged during the follow-up period. Serial ultrasonography, however, showed a progressive increase in the size and echogenic alteration of the largest mass in the left lobe, suggesting a malignant transformation. The largest nodule became heterogeneous with a thin hypoechoic rim 13 months later (Fig. 2 middle). However, ultrasonographic findings of other small nodules, especially in the right lobe, suggested a benign hepatic adenoma. The high density mass in the left lobe (Fig. 3 upper) showed a low density area measuring 3 cm in diameter on CT scan (Fig. 3 middle). A dynamic CT scan disclosed that the tumor had enhanced rapidly to become hyperdense, followed by a gradual decline in density. At this time (April 7, 1992), the specimens biopsied from the largest mass disclosed normal appearing liver cells without bile ducts or portal areas, consistent with hepatic adenoma (Fig. 4). An operation was not performed, because of the multiple hepatic lesions, and the patient was again followed using ultrasonographic examinations. Her renal function gradually deteriorated during this observation period, and she was obliged to undergo hemodialysis at another hemodialysis center. Seven and half years later, she was referred again to our hospital to apply for kidney transplantation. At the time of this report (April 27, 2000), laboratory data showed fasting blood sugar at 75 mg/dl, serum uric acid at 8.1 mg/dl, serum creatinine at 6.4 mg/dl, urea nitrogen at 48.0 mg/dl, glucagon 79 pg/ml, and lactic acid at 16.2 mg/dl. Interestingly, the most recent
Regression on Hepatic Adenoma

Figure 2. Change in the appearance of the tumor on abdominal ultrasonogram. Upper: Hypoechoic mass, measuring 12×16 mm, is demonstrated in the left liver lobe. Middle: Alteration in echogenicity of the hepatic tumor in the left lobe is shown. The hepatic tumor became heterogeneous with a thin hypoechoic rim 13 months later. Lower: Regression of the hepatic tumor in the left lobe after 8 years and a course of hemodialysis is shown.

Figure 3. Change in the appearance of the tumor on abdominal computed tomogram. Upper: Small high density area is present in the left lateral segment of the liver on abdominal CT scan. Middle: The left lobe hepatic tumor appears as a low density area on an abdominal CT scan taken 13 months later. Lower: The left lobe hepatic tumor is invisible on an abdominal CT scan taken 8 years later.
Detection of hepatic adenoma in patients with GSD-type I

Sumitomo et al (1) reviewed 50 cases of hepatic tumors as-

Figure 3 lower). adenoma in the left lateral segment of the liver (Fig. 2 lower; ultrasonography and CT scan demonstrated a regression of the

mentioned that the presence of an echogenic or heterogeneous

ultrasonographic appearance of GSD-type I hepatic adenomas has
enomas associated with GSD-type I have been described as
eraged premalignant, therefore, it is imperative that all GSD-type

in size and number of tumors, and a loss of demarcation of the
tumors. In the present case, the ultrasonographic appearance
of the tumor changed from hypoechoic to heterogeneous, and
the CT appearance changed from hyperdense to hypodense with
an increase in size. Although both of these interesting findings
were difficult to differentiate from malignant transformation, a
tissue diagnosis suggested hepatic adenoma.
The pathogenesis of hepatic adenoma in GSD-type I remains
incompletely understood, though the association between he-
patic adenoma and the use of oral contraceptives is well known.
Recurrent and prolonged hypoglycemia with secondary stimu-
lation such as glucagon, epinephrine, or insulin has been pos-
tulated to be responsible for the development of hepatic ad-
enoma in GSD-type I. In contrast, however, a regression of
hepatic adenomas with dietary therapy or nightly glucose infu-
sion has been reported (9). Correction of the glucose/insulin
ratio, glycogen overload, and abnormal long-fatty acid metabo-
ism may be associated with the resolution of hepatic adenoma. The present case also showed a natural regression 8 years later,
but the exact mechanism of regression remains unclear, since
the hypoglycemia was mild and the patient did not require spe-
cial dietary therapy or nightly glucose infusion. It is possible
that hemodialysis may have had some favorable effect, by cor-
recting some metabolic imbalance.

In conclusion, late complications such as gout, hyperlipi-
demia, and hepatic tumor are considered important prognostic
factors for longer survival in GSD-type I. Particularly, multi-
centric hepatic adenomas seen by ultrasonography are consid-
ered premalignant, therefore, it is imperative that all GSD-type
I patients be closely followed by the use of ultrasonography or
CT scan, and further, that correction of metabolic imbalance,
such as hypoglycemia with dietary therapy, should be done as
early as possible to prevent the development of hepatic ad-
enomas or induce their resolution.

Discussion

Sumitomo et al (1) reviewed 50 cases of hepatic tumors as-

associated with GSD-type I in 1988. Among them, a histological
diagnosis of the tumor was documented in 22 cases. They con-
sisted of 16 cases of hepatic adenoma (73%), 3 cases of hepa-
tocellular carcinoma (14%), 2 cases of focal nodular hyperpla-
sia (FNH) (9%), and 1 case of hepatoblastoma (4%). Occur-
rences of hepatic adenoma in GSD-type I have been exten-
sively studied since the first case was reported in 1955 (2). The
development of GSD-type I adenomatous nodules in the liver
has been regarded as an infrequent occurrence, however, a re-
cent report suggested a higher incidence (50–80%), particu-
larly in patients who are over 10 years of age (3).

Detection of hepatic adenoma in patients with GSD-type I
have been accomplished with the use of ultrasonography, he-
patic scintigraphy, and computed tomography. However, in view
of their sensitivity for detection of small hepatic lesions, ultra-
onography or computed tomography is superior to hepatic
scintigraphy. On ultrasonography, a hepatic adenoma
unassociated with glycogen storage disease is echogenic, with
or without hypoechoic components. However, hepatic ad-
enomas associated with GSD-type I have been described as
hypoechoic (4), and in larger adenomas a heterogeneous
echogenic or hypoechoic pattern has been observed along with
the overall echogeneity (5), which is presumed to be second-
ary to necrosis, hemorrhaging or both, though the ultra-
onographic appearance of GSD-type I hepatic adenomas has
been described in only a few reports. Bowerman et al (6) also
mentioned that the presence of an echogenic or heterogeneous
solid mass with enhanced sound transmission suggests hepatic
adenoma in a GSD-type I patient. Moreover, a few studies have
reported CT findings of the liver in GSD-type I. Hepatic ad-
enomas in GSD-type I show no consistent features on a pre-
contrast CT scan. Some are hypodense (7), while others are
hyperdense or isodense (8), though a hepatic adenoma may be
suggested when hemorrhage foci are detected. Unfortunately,
reports concerning the CT features of hepatic adenoma in GSD-
type I are too few to give sufficient precise information, there-
fore it may be difficult at this time to diagnose hepatic adenoma
on CT findings alone. In contrast, a dynamic CT scan seems to
give significant information for obtaining an exact diagnosis.
Rapid enhancement to hyperdensity followed by a slow de-
cline in density allows a reliable diagnosis, and an accumula-
tion of imaging examination results for hepatic adenoma and/
or carcinoma in GSD-type I will serve to provide guidelines
for a correct diagnosis.

Hepatic adenoma in GSD-type I is considered to be a pre-
malignant lesion, as it has been reported that some patients
with adenoma develop hepatocellular carcinomas later (8).
Malignant transformation has been suggested, with an increase
in size and number of tumors, and a loss of demarcation of the
malignant lesion, as it has been reported that some patients
with adenoma develop hepatocellular carcinomas later (8).
Malignant transformation has been suggested, with an increase
in size and number of tumors, and a loss of demarcation of the
original report suggested a higher incidence (50-80%), particu-
larly in patients who are over 10 years of age (3).

Discussion

Sumitomo et al (1) reviewed 50 cases of hepatic tumors as-

associated with GSD-type I in 1988. Among them, a histological
diagnosis of the tumor was documented in 22 cases. They con-
sisted of 16 cases of hepatic adenoma (73%), 3 cases of hepa-
tocellular carcinoma (14%), 2 cases of focal nodular hyperpla-
sia (FNH) (9%), and 1 case of hepatoblastoma (4%). Occur-
rences of hepatic adenoma in GSD-type I have been exten-
sively studied since the first case was reported in 1955 (2). The
development of GSD-type I adenomatous nodules in the liver
has been regarded as an infrequent occurrence, however, a re-
cent report suggested a higher incidence (50–80%), particu-
larly in patients who are over 10 years of age (3).

Detection of hepatic adenoma in patients with GSD-type I
have been accomplished with the use of ultrasonography, he-
patic scintigraphy, and computed tomography. However, in view
of their sensitivity for detection of small hepatic lesions, ultra-
onography or computed tomography is superior to hepatic
scintigraphy. On ultrasonography, a hepatic adenoma
unassociated with glycogen storage disease is echogenic, with
or without hypoechoic components. However, hepatic ad-
enomas associated with GSD-type I have been described as
hypoechoic (4), and in larger adenomas a heterogeneous
echogenic or hypoechoic pattern has been observed along with
the overall echogeneity (5), which is presumed to be second-
ary to necrosis, hemorrhaging or both, though the ultra-
onographic appearance of GSD-type I hepatic adenomas has
been described in only a few reports. Bowerman et al (6) also
mentioned that the presence of an echogenic or heterogeneous
solid mass with enhanced sound transmission suggests hepatic
adenoma in a GSD-type I patient. Moreover, a few studies have
reported CT findings of the liver in GSD-type I. Hepatic ad-
enomas in GSD-type I show no consistent features on a pre-
contrast CT scan. Some are hypodense (7), while others are
hyperdense or isodense (8), though a hepatic adenoma may be
suggested when hemorrhage foci are detected. Unfortunately,
reports concerning the CT features of hepatic adenoma in GSD-
type I are too few to give sufficient precise information, there-
fore it may be difficult at this time to diagnose hepatic adenoma
on CT findings alone. In contrast, a dynamic CT scan seems to
give significant information for obtaining an exact diagnosis.
Rapid enhancement to hyperdensity followed by a slow de-
cline in density allows a reliable diagnosis, and an accumula-
tion of imaging examination results for hepatic adenoma and/
or carcinoma in GSD-type I will serve to provide guidelines
for a correct diagnosis.

Hepatic adenoma in GSD-type I is considered to be a pre-
malignant lesion, as it has been reported that some patients
with adenoma develop hepatocellular carcinomas later (8).
Malignant transformation has been suggested, with an increase
in size and number of tumors, and a loss of demarcation of the
tumors. In the present case, the ultrasonographic appearance
of the tumor changed from hypoechoic to heterogeneous, and
the CT appearance changed from hyperdense to hypodense with
an increase in size. Although both of these interesting findings
were difficult to differentiate from malignant transformation, a
tissue diagnosis suggested hepatic adenoma.
The pathogenesis of hepatic adenoma in GSD-type I remains
incompletely understood, though the association between he-
patic adenoma and the use of oral contraceptives is well known.
Recurrent and prolonged hypoglycemia with secondary stimu-
lation such as glucagon, epinephrine, or insulin has been pos-
tulated to be responsible for the development of hepatic ad-
enoma in GSD-type I. In contrast, however, a regression of
hepatic adenomas with dietary therapy or nightly glucose infu-
sion has been reported (9). Correction of the glucose/insulin
ratio, glycogen overload, and abnormal long-fatty acid metabo-
lism may be associated with the resolution of hepatic adenoma. The present case also showed a natural regression 8 years later,
but the exact mechanism of regression remains unclear, since
the hypoglycemia was mild and the patient did not require spe-
cial dietary therapy or nightly glucose infusion. It is possible
that hemodialysis may have had some favorable effect, by cor-
recting some metabolic imbalance.

In conclusion, late complications such as gout, hyperlipi-
demia, and hepatic tumor are considered important prognostic
factors for longer survival in GSD-type I. Particularly, multi-
centric hepatic adenomas seen by ultrasonography are consid-
ered premalignant, therefore, it is imperative that all GSD-type
I patients be closely followed by the use of ultrasonography or
CT scan, and further, that correction of metabolic imbalance,
such as hypoglycemia with dietary therapy, should be done as
early as possible to prevent the development of hepatic ad-
enomas or induce their resolution.
Regression on Hepatic Adenoma

References


