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Clinical Note

# Hepatocellular carcinoma with glycogen storage disease type 1a

Running title: Hepatocellular carcinoma with GSD 1a

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**Key words:** glycogen storage disease, hepatic adenoma, hepatocellular carcinoma, PIVKA-II

A female patient was diagnosed with glycogen storage disease type 1a (GSD Ia) by genetic tests at 4 years of age. Her case was followed up by a pediatrician at another hospital. Since the age of 17 years, frequent vomiting due to gastroesophageal reflux (GER) was observed, and therefore, medical treatment was initiated. Ultrasonography revealed a hepatic tumor with a diameter 9 cm, which was suspected as hepatic adenoma (HA). There was no elevation in the levels of serum α fetoprotein (AFP, 1.6ng/ml), carcinoembryonic antigen (CEA, 1.0ng/dl), and protein adducts in the absence of vitamin K (PIVKA-II; 37 mAU/ml). In addition, early phase arterial enhancement with early washout in enhanced CT was not observed (Figure 1 A,B). The patient was followed-up every 6 months by ultrasonography. A slightly enlarged HA was observed at the age of 18 years (maximum diameter was 9.5 cm; serum tumor makers were not monitored at that time). As GER symptoms worsened at the age of 19 years, we planned to perform fundoplication and gastrostomy. Preoperative dynamic CT revealed that the diameter of the hepatic tumor increased to 11 cm, and early arterial enhancement with relatively early wash out was observed (Figure 1 C,D). Laboratory data revealed that aspartate aminotransferase (15 IU/l), alanine aminotransferase (7 IU/l), alkaline phosphatase (379 U/l), serum total bilirubin (0.1 mg/dl), prothrombin time (11.6 s), and AFP (2.1 ng/ml) were all within normal limits; however, PIVKA-II (208 mAU/ml) was elevated. Analysis of CT images and blood test findings comprehensively pointed toward HCC. We therefore decided to perform hepatic tumor resection and fundoplication simultaneously. Under laparotomy, S4,5 resection, fundoplication and gastrostomy creation were performed. No complications associated with GSD Ia were observed during the surgery.

Pathological evaluation of the resected specimen revealed that the hepatic tumor contained well differentiated thin trabecular type hepatocellular carcinoma (HCC) which was found in the background of HA (see supporting information). The patient did not exhibit any symptom

or recurrence of tumor for 6 years post-surgery.

GSD Ia is caused by a deficiency in glucose-6-phosphatase, that results in excessive accumulation of glycogen in the liver, kidney, skeletal muscles, and intestinal mucosa. HA is a well-known complication associated with GSD Ia, which develops in the second to third decade of life with a mean age between 11 to 19 years. Since patients with GSD Ia live longer, HCC has been noted as a long term complication in several patients with GSD Ia.[1-4] However, the natural history and pathophysiology of the disease condition remain poorly understood.[1-5] A practice guideline recommended that in individuals with GSD Ia, liver ultrasounds should be performed to test for HAs every 12-24 months: and with increasing age, CT or MRI should be performed to detect evidences of increasing lesion.[3] However, most studies suggest that the detection of the malignant transformation of HA to HCC using imaging studies in GSD 1a patients still remains a challenge. In addition, there are also no effective tumor markers since AFP and CEA levels are often normal even on the onset of HCC, and other tumor markers such as PIVKA-II and glypican-3 have not been studied in children with GSD Ia.[1, 3-5]

In the present case study, we serendipitously detected HA in the patient at the age of 17 years, and continued follow-up observations despite the growth in tumor size. According to our findings from dynamic contrast CT (Figure 1) and a slight increase in PIVKA-II observed during preoperative evaluation, we decided to perform hepatectomy and fundoplication simultaneously. The patient was pathologically diagnosed HCC as an outcome. Although, in this case, tumor resection provided the requisite curative measure, tumor markers could have been monitored and contrast CT could have been performed at the age of 18 years, since the time course of malignant transformation of the tumor to HCC during the follow-up period was unclear.

We believe that this case highlights the importance of long-term follow-up with contrast CT and serum tumor markers in the consideration of potential malignant transformation of

hepatic adenoma in patients with GSD Ia. We suggest that PIVKA-II could be one of the reliable tumor markers which could detect malignant changes from HA to HCC in patients with hepatic adenoma combined with GSD Ia.

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All data were collected anonymously, and patient consent was obtained from the mother of patient. The Ethics Committee at Kobe University Hospital/Kobe University Graduate School of Medicine confirms that ethics approval for this case report is waived.

**Authors' contributions**

Y.O. and T.H managed the patient and contributed to the conceptualization of the manuscript; Y.O. drafted the manuscript; and Y.A, Y.T, T.H, Y.B., and Y.O. reviewed the manuscript. All authors read and approved the final manuscript.

**Conflict of interest**

The authors declare no conflict of interest.

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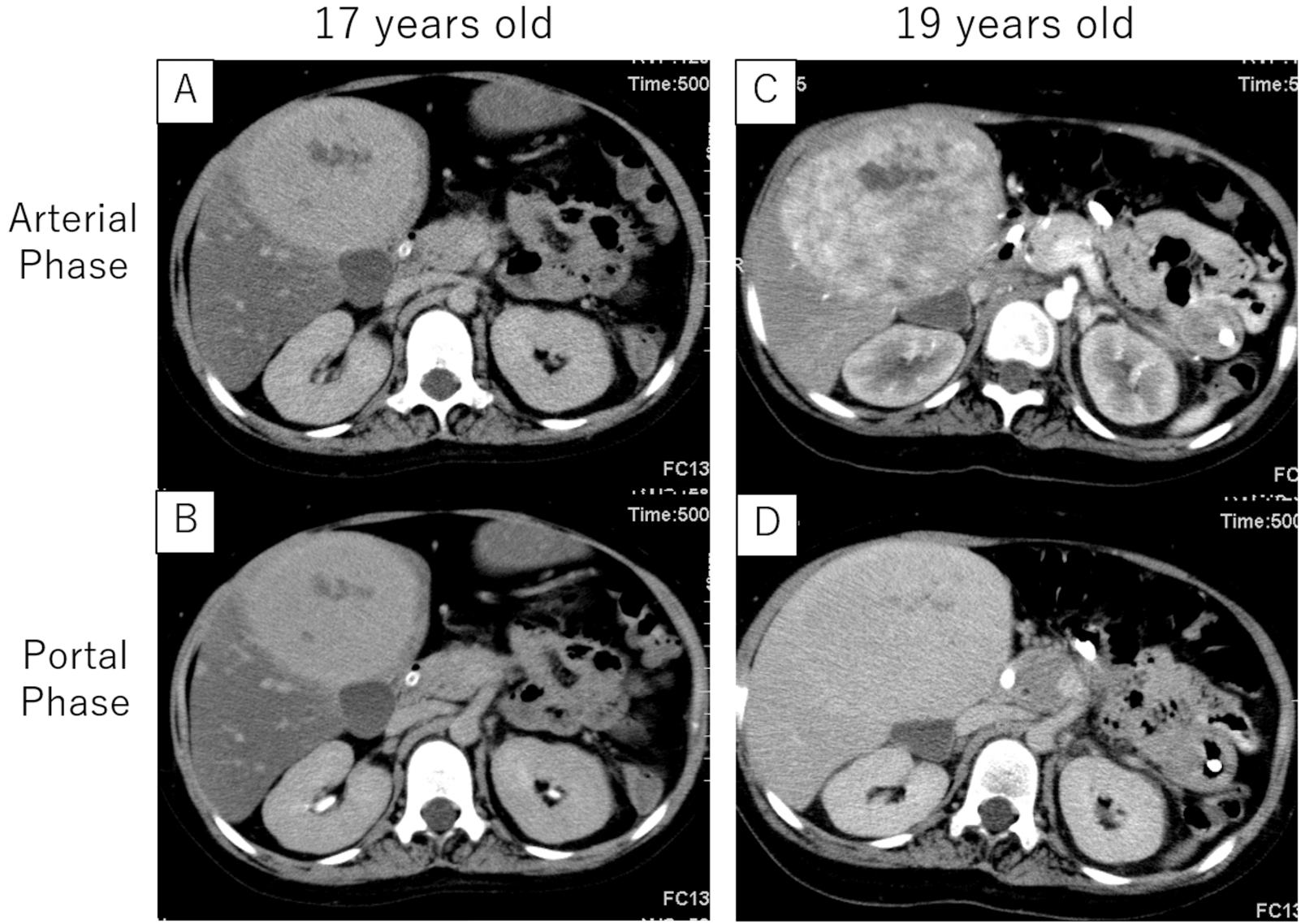
**Figure Legend**

**Figure 1.** (A, B) The lack of difference in contrast enhancement between arterial and portal phases of dynamic CT at 17 years of age. (C, D) Arterial and portal phases of dynamic CT at 19 years of age. A slight hyper-enhancement of the nodule in the arterial phase and washout in the portal venous phases were observed.

**Supporting information**

The pathological images of a resected hepatic tumor. (a) A photograph of the cut surface shows a yellowish-white, solid tumor. (b, c) Histological characteristics of hepatocellular carcinoma: the hepatocellular carcinoma was found in the background of hepatic adenoma. The areas that transformed into well-differentiated hepatocellular carcinoma show more distinct nuclear atypia and crowding due to an increased nucleo-cytoplasmic ratio and thickening of the trabecules. (b) HE stain, 200× magnification, (c) silver impregnation stain, 200× magnification.


17 years old
19 years old
Arterial Phase
Portal Phase
A
B
C
D
Time:500
Time:5
FC13
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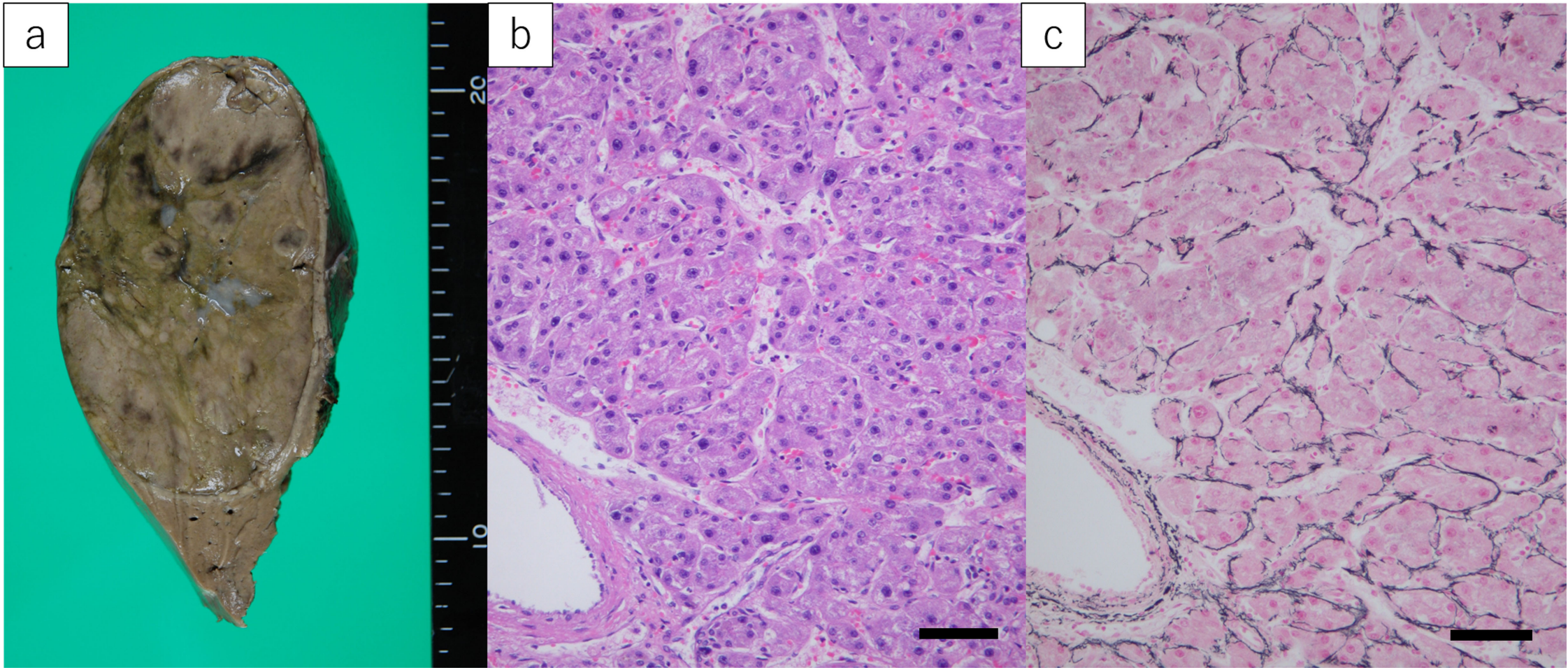
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b
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