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Case Report

Hepatocellular Carcinoma Diagnosed by Routine Abdominal Ultrasound Examination during Pregnancy

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Summary

A case in which HCC was diagnosed by an abdominal ultrasound examination conducted as part of a routine examination during pregnancy, and the patient then underwent cesarean section at 34 weeks' gestation and hepatectomy on the same day is presented.

A 37-year-old woman was found to be hepatitis B surface (HBs) antigen-positive at a routine checkup in the 12th week of pregnancy. She was diagnosed as an inactive hepatitis B virus (HBV) carrier and underwent abdominal ultrasound examination, which found no liver tumor. However, further abdominal ultrasound at 30 weeks' gestation showed an irregular tumor in the right lobe of the liver. Based on the ultrasound findings, the tumor was diagnosed as HCC. There was no evidence of metastases. A cesarean section followed by S5 partial hepatectomy was performed at 34 weeks 3 days of gestation. Ultrasound screening for HCC of pregnant women who are HBV carriers is very important for both mother and child.

Key Words: hepatocellular carcinoma, pregnancy, ultrasound examination

1. Introduction

Hepatocellular carcinoma (HCC) rarely develops during pregnancy. This may be because the incidence of HCC is low in women of child-bearing age, or because infertility is common in patients with liver cirrhosis, which is a cause of HCC[1)].

A case in which HCC was diagnosed by abdominal ultrasound conducted as part of a routine examination during pregnancy, and the patient underwent cesarean section at 34 weeks' gestation and hepatectomy on the same day is presented.

Ultrasound screening for HCC of pregnant women who are HBV carriers is very important for both mother and child.

2. Case Presentation

A 37-year-old woman was found to be hepatitis B surface (HBs) antigen-positive at a routine checkup in the 12th week of natural pregnancy. She was seen at a

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Table 1 Laboratory data

Blood chemistry		Viral markers	
AST	20 U/dl	HBs Ag	842.6 IU/ml
ALT	14 U/dl	HBs Ab	< 1.0 mIU/ml
ALP	337 U/dl	HBc Ab	> 200 C.O.I
LDH	152 U/dl	HBe Ag%	100 %
GGT	12 U/dl	HBV DNA	2.5 LogIU/ml
T-Bil	0.53 mg/dl	HBV Genotype	C
TP	6.4 g/dl	HCV Ab	(−)
Alb	2.92 g/dl		
Hematological analysis		**Tumor markers**	
WBC	7.3×10^3 /l	AFP	16121 ng/ml
RBC	348×10^4 /l	AFP-L3	2.5 %
Hgb	10.9 g/dl	PIVKA II	177 mAU/ml
Plt	23×10^4 /l		
PT	129 %		

AST; Aspartate aminotransferase, ALT; Alanine aminotransferase, ALP; Alkaline phosphatase, LDH; Lactate dehydrogenase, GGT; γ-glutamyl transpeptidase, T-Bil; Total bilirubin, TP; Total protein, Alb; Albumin, WBC; White blood cells, RBC; Red blood cells, Hgb; Hemoglobin, Plt; Platelet, PT: Prothrombin time, AFP; α-fetoprotein, PIVKA II; Protein induced by vitamin K absence-II, HBs; Hepatitis B surface, HBc; Hepatitis B core, HBe; Hepatitis B envelope, Ag; Antigen, Ab; Antibody, HBV; Hepatitis B virus, HCV; Hepatitis C virus.

specialist gastrointestinal clinic and diagnosed as a hepatitis B virus (HBV) carrier, and she underwent abdominal ultrasound examination. When this investigation was conducted, there was no morphological abnormality of the liver, and no liver tumor was detected. Although the patient was asymptomatic, the gastrointestinal specialist conducted a further abdominal ultrasound at 30 weeks' gestation. During this ultrasound, they identified a tumor in the right lobe of the liver, and she was then further examined in our hospital. Her previous medical history was unremarkable, and there was no family history of liver disease. She had never smoked, drank significant amounts of alcohol, nor used illegal drugs.

Blood test results on initial examination are shown in Table 1. The values of aspartate aminotransferase and alanine aminotransferase were within the normal range, and no liver dysfunction was apparent. HBs antigen was positive, hepatitis B core (HBc) antibody was high-titer positive, and the patient was diagnosed as an HBV carrier. The HBV DNA level was low at 2.5 LogIU/ml, and she was presumed to be an inactive carrier. The HBV genotype was C. The value of α-fetoprotein (AFP) was elevated at 16,121 ng/ml, but the AFP-L3 fraction was within the normal range, and whether the elevated AFP was due to the tumor or to pregnancy could not be distinguished. Protein induced by vitamin K absence or antagonist-II (PIVKA-II) was moderately elevated, at 177 mAU/ml.

Fig. 1 shows the abdominal ultrasound image taken at our hospital. An irregular tumor with a maximum diameter of 6 cm was protruding out of the liver from the surface of segment 5. Although there was no marginal hypoechogenicity (halo) or lateral shadow, a mosaic pattern was evident inside the tumor (Fig. 1A). On Doppler ultrasound, a pulsating perfusion signal was evident inside the tumor (Fig. 1B). On contrast-enhanced ultrasound using perflubutane microbubbles, the tumor was homogeneously intensely stained during the early vascular phase (left side of Fig. 1C), but it was hypoechoic compared with the surrounding liver during the Kupffer phase (right side of Fig. 1C). Based on these ultrasound findings, the tumor was diagnosed as HCC. There were no signs of chronic liver disease

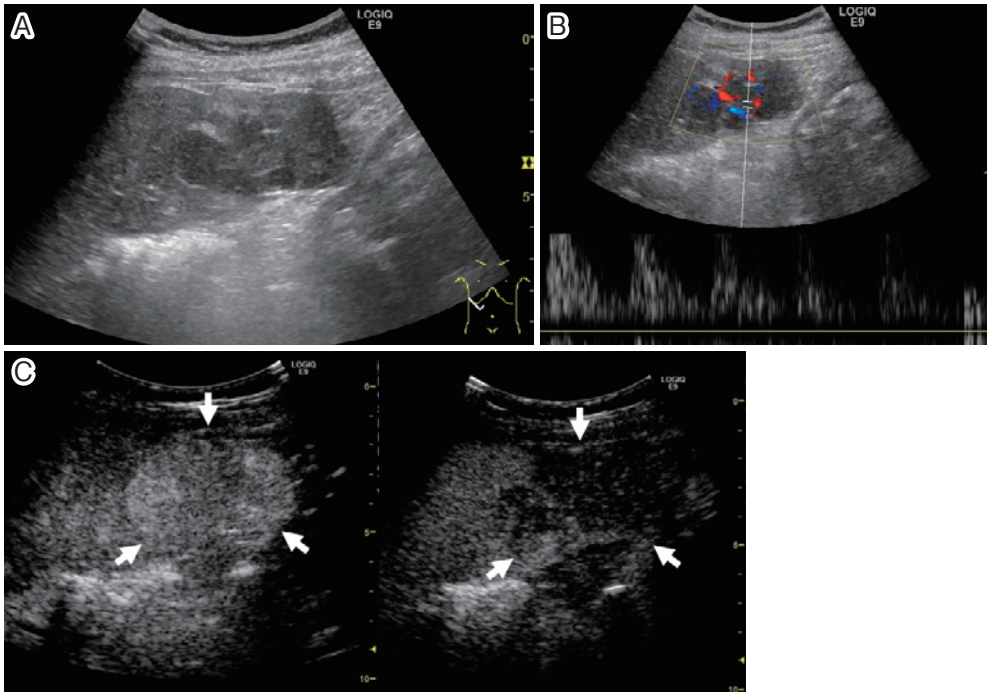

Figure 1 Abdominal ultrasound images

An abdominal ultrasound scanned during the initial examination at our hospital shows an irregular tumor with a maximum diameter of 6 cm protruding out of the liver from the surface of segment 5. **A:** Although there is no marginal hypoechogenicity (halo) or lateral shadow, a mosaic pattern is evident inside the tumor. **B:** On color Doppler ultrasound, an intense pulsating perfusion signal is evident inside the tumor. **C:** On contrast-enhanced ultrasound using perflubutane microbubbles, the tumor is homogeneously intensely stained during the early vascular phase (arrows on the left side of **C**), but it is hypoechoic compared with the surrounding liver during the Kupffer phase (arrows on the right side of **C**).

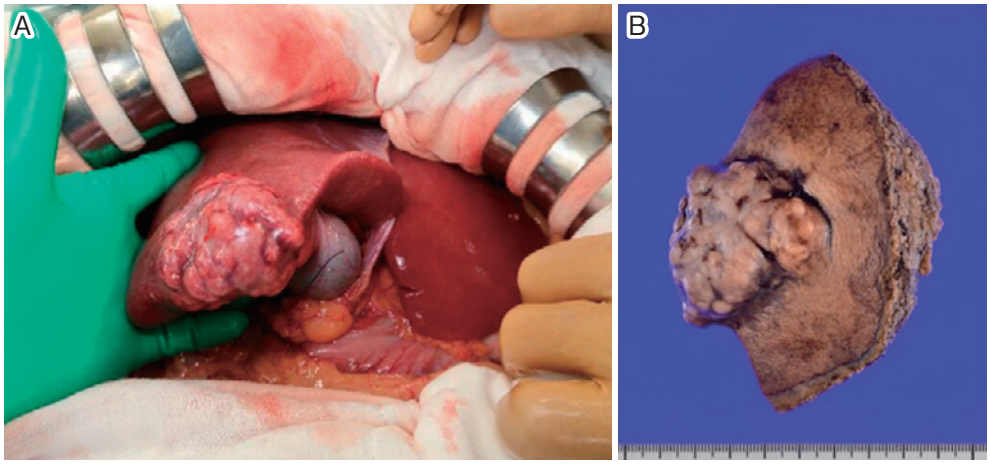

Figure 2 Intraoperative images

A: After the abdomen has been opened, a tumor protruding into the peritoneal cavity from segment 5 of the liver is observed. **B:** The cut surface of the resected specimen shows it to be a multinodular tumor.

in the background liver, and hepatorenal contrast was negative. Detailed observations in B mode and the contrast Kupffer phase were performed, but no intrahepatic metastasis was observed. There were no signs of tumor thrombus in the portal vein or bile duct.

Plain thoracic computed tomography (CT) and plain abdominal magnetic resonance imaging (MRI) were conducted, and the absence of distant metastasis was confirmed.

On the basis of the above results, HCC cT2N0M0

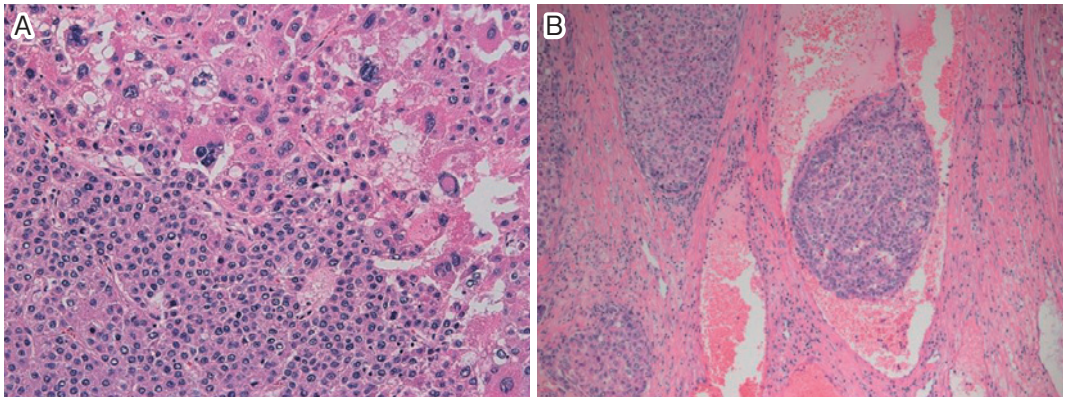

Figure 3 Histopathological presentation

A: The majority of the tumor consists of moderately differentiated HCC (lower left). It shows a typical growth pattern of thick trabeculae. In addition, there is a component of poorly differentiated HCC in a localized area (upper right). In this area, tumor cells have marked nuclear atypia with bizarre nuclei (H&E, ×200).

B: Venous invasion is observed (H&E, ×100).

(cStage II) was diagnosed.

A cesarean section followed by S5 partial hepatectomy was performed at 34 weeks 3 days of gestation. Consistent with the ultrasound findings, the tumor was protruding from segment 5 of the liver (Fig. 2A), and its cut surface showed it to be a multinodular tumor (Fig. 2B). The surface of the liver of the non-tumor part was smooth, and edge was sharp.

Fig. 3 shows the histopathological presentation. The majority of the tumor consisted of moderately differentiated HCC. In addition, there was a component of poorly differentiated HCC in a localized area (Fig. 3A), and mitotic figures were also observed. The resection margins were negative, and the tumor had been resected *en bloc*. Mild venous invasion (Vv1) was present (Fig. 3B), and the final pathological diagnosis was pT3N 0M0 stage III. The liver tissue of the non-tumor part showed extremely mild lymphocytic infiltration and there was no fibrosis.

The patient's postoperative course was uneventful, and she was discharged on postoperative Day 11. The infant weighed 1,858 g at delivery. Hepatitis B immunoglobulin and HB vaccine were administered, and the child was discharged on Day 41 after birth. Tenofovir alafenamide fumarate administration for HBV infection was started post-discharge. Blood tests at 1 month postoperatively showed that tumor markers had decreased markedly, with AFP 152 ng/ml and PIVKA-II 20 mAU/ml. At 2 months postoperatively, however, AFP was again elevated at 2776 ng/ml, although PIVKA-II remained at 20 mAU/ml. Contrast CT showed multiple small tumors in both lobes of the liver, and HCC recurrence was diagnosed. At the time this paper was submitted, the patient was continuing chemotherapy at another specialist medical institution.

3. Discussion

HCC during pregnancy was first reported by Wilson *et al.* in 1957[2], and in 1995, Lau *et al.* investigated 28 cases and reported that its prognosis is extremely poor[3]. The reasons are known to include the limitations on investigations and treatment imposed by pregnancy, as well as the fact that the physiological symptoms of pregnancy, including fatigue, abdominal pain, nausea, and vomiting, resemble those of HCC, and its diagnosis may therefore be delayed[4].

Tumors grow rapidly during pregnancy as a result of diminished immune function and activated estrogen[5,6]. Diminished immune function is a factor that encourages tumor progression. Estrogen has been shown to cause mitotic division by hepatocytes, vascular dilation, increased free radicals, hepatitis B virus reactivation, and decreased humoral immunity[7].

The treatment strategy for malignant neoplasms discovered during pregnancy must take into account the wellbeing of both mother and fetus. During the first trimester of pregnancy, maternal survival is normally prioritized. If resection is delayed until the 28th week, when the fetus is capable of survival, it is likely that the life of both the mother and the fetus cannot be

guaranteed, with the risks including tumor rupture as a result of rapid tumor growth, and the usual recommendation is therefore to terminate the pregnancy and perform hepatectomy. From the second trimester, anesthesia is safe for the fetus, and hepatectomy can therefore be attempted while the pregnancy is maintained[8].

In a 2011 study, Choi *et al*. investigated 48 cases and reported that, since 1995, the capacity to diagnose HCC during pregnancy had increased, and that its prognosis had also improved thanks to surgery and other therapeutic interventions[4]. A case has recently been reported of a patient diagnosed with HCC in the second trimester who continued the pregnancy while undergoing radiofrequency ablation therapy, with hepatectomy conducted after delivery. This has attracted attention as a future new treatment strategy[9]. Cases of the long-term survival of patients who have aborted the pregnancy and subsequently undergone hepatectomy have also been reported, and the treatment of HCC in pregnancy must involve discussion with a team of wide-ranging specialists and obtaining appropriate informed consent from the patient and her family members[10].

The present patient was found to be HBs antigen-positive at 12 weeks' gestation, and an abdominal ultrasound was therefore performed, but no liver tumor was detected. The materials available to us did not include a clear image of the margin of segment 5 of the liver, but the physician who conducted the ultrasound is an experienced liver specialist who is unlikely to have overlooked a tumor. Although the patient was asymptomatic, another ultrasound was conducted at 30 weeks on the judgement of that physician. As a result of the detection of a liver tumor in that second investigation, a 6-cm HCC was diagnosed. The fact that mitotic figures were observed on pathological examination also suggested that the tumor was fast-growing. If the second ultrasound had not been conducted, it might well have become untreatable.

Contrast-enhanced ultrasound was chosen for definitive diagnosis and the assessment of perfusion. As shown in Fig. 1, there was abundant arterial perfusion, and the fact that the tumor was growing as a protrusion outside the liver meant that the risk of intraperitoneal rupture was judged to be extremely high. At 32 weeks' gestation, the infant could be delivered, and it was therefore decided to proceed with an immediate cesarean section and hepatectomy. The tumor was resected *en bloc*, but although tumor marker levels subsequently decreased, they were again elevated within a few months, and recurrence was confirmed by CT. The tumor was highly malignant, being mostly moderately differentiated with a poorly differentiated area, and the fact that venous invasion had occurred may also have been a factor in its recurrence.

According to recent reports, 0.7%-0.9% of the Japanese population are positive for the HBs antigen[11,12]. Other studies have found that 0.51%-1.75% of pregnant women in Japan are HBs antigen-positive, a rate equivalent to or somewhat higher than the general prevalence[13-15]. Most cases of HCC in pregnancy are caused by HBV[8-10,16,17]. In the present case, the identification of the patient as HBs antigen-positive using a routine examination during pregnancy was what led to the diagnosis of HCC. And this case has neither chronic hepatitis or cirrhosis.

This case indicates the great importance of ultrasound screening for HCC of pregnant women who are HBV carriers. In pregnant women who are HBV carriers, ultrasonography should be performed all over the course of pregnancy, not only at initial diagnosis.

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Data Availability

The access to data used to support this study is permitted with the author's permission.

Consent

Informed consent was obtained from the patient for publication purposes.

Author Contributions

Hayakawa F reviewed the literature and contributed to manuscript drafting; Kusano Y and Ota T analyzed and interpreted the imaging findings; Suzuki K performed the infectious diseases consultation, reviewed the literature and drafted the manuscript; Noro T and Yoshitomi H were the patient's surgeon, reviewed the literature and contributed to manuscript drafting; Tamano M was responsible for the revision of the manuscript for important intellectual content; all authors issued final approval for the version to be submitted.

Conflict of Interest

The authors have no conflicts of interest directly relevant to the content of this article.

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