A Case Report of Primary Hepatic Squamous Cell Carcinoma That Remarkably Responded to Low Dose Arterial Injection of Anti-Cancer Drugs

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Summary: Primary hepatic squamous cell carcinoma is rare. In this case, a malignant lesion was detected in bilateral hepatic lobes by ultrasound sonography and computed tomography. The maximum tumor diameter was approximately 10 cm. Tumor tissue obtained by aspiration liver biopsy was diagnosed as poorly differentiated squamous cell carcinoma. In gallium radioisotope scanning, no focus was detected in any organs other than the liver. As therapy, anti-cancer drugs were administered via hepatic arterial infusion. The patient received 10 mg of cis-diaminedichloro-platinum (CDDP) and 250 mg of 5-fluorouracil (5-FU) for 5 days every week. The therapy was continued for 3 weeks, and the same doses of CDDP and 5-FU were given to the patient once per 2 weeks in the clinic. The intrahepatic tumor lesion began to decrease from the start of treatment, and had almost disappeared 8 months after. Recurrence of the liver tumor occurred at 12 months from the start of treatment. The patient was re-admitted and treated with the same anti-cancer drugs via hepatic arterial injection. However, the drugs showed remarkable effect no longer and she died in month 23. The treatment with chemotherapy via hepatic arterial injection for a patient with squamous cell carcinoma offered a favorable therapeutic effect.

Key words primary hepatic squamous cell carcinoma, anti-cancer drugs, low dose arterial injection

INTRODUCTION
Primary hepatic squamous cell carcinoma is a very rare disease. Here, we report a case treated with a combinational chemotherapy using CDDP and 5-FU via hepatic arterial injection, which produced a prolonged survival.

CASE REPORT
A 67-year-old female was referred to our hospital for recent aggravation of general fatigue and a slight fever. From a few days before admission, an antibiotic agent had been given. However, no improvement in the fever was observed. Her medical history did not reveal any systemic diseases, and her family history was noncontributory. Physical examination was remarkable for hepatomegaly five finger breadths below the right costal margin and three finger breadths below the epigastric margin, as well as for icterus in bulbar conjunctiva. Results of laboratory tests included red blood cell count $319 \times 10^4/\text{mm}^3$. 

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Abbreviations: AFP, $\alpha$-fetoprotein; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CA19-9, carbohydrate antigen 19-9; CDDP, cis-diaminedichloro-platinum; CEA, carcinoembryonic antigen; CPK, creatine phosphokinase; $\gamma$-GTP, $\gamma$-glutamyl transpeptidase; 5-FU, 5-fluorouracil; LDH, lactate dehydrogenase; T. Chol., total cholesterol; ZTT, zinc sulfate turbidity test.
hemoglobin 10.1 g/dL, hematocrit 31.4%, white blood cell count 13,900/mm³, platelets 478×10³/mm³, and urinary urobilinogen (3+).

**Blood chemistry**

AST 56 IU/L, ALT 43 IU/L, LDH 1225 IU/L, ALP 527 IU/L, γ-GTP 128 IU/L, T-Chol. 213 mg/dL, Total protein 8.2 g/dL, albumin 4.5 g/dL, α1-globulin 8.0%, α2-globulin 19.7%, β-globulin 9.5%, γ-globulin 19.5%. Total bilirubin 3.0 mg/dL, ZTT 8.4 U, CPK 186 IU/L, Amylase 49 IU/L, BUN 9.3 mg/dL, Creatinin 0.8 mg/dL, Na 136 Meq/mL, K 3.7 Meq/mL, Cl 106 Meq/mL, Glucose 106 mg/dL, Fe 11 μg/dL, Prothrombin time 85%. Tumor marker: AFP 2.9ng/mL, CEA 2.1ng/mL, CA19-9 10 U/mL, SCC 210 ng/mL, Virus Marker: Hepatitis B virus surface antigen: negative, Hepatitis C virus antibody: negative

**Abdominal ultrasound examination**

A massive space-occupying lesion, where of the surrounding area is irregular and the inside shows a hypoechoic and heterogeneous pattern, was localized in the right lobe (Fig. 1). Moreover, swelling of hepatic hilar lymph nodes was recognized (not shown), but dilatation of intra- and extra-hepatic bile ducts was not.

**Abdominal X-ray dynamic computed tomography**

The margin of the space-occupying lesion, which was localized in the right lobe, was detected by a contrast enhance effect in the arterial phase using a contrast agent (Fig. 2a). However, the contrast enhance effect disappeared in the delayed venous phase (Fig. 2b). A few lymph nodes near by the hepatic hilus were enlarged (not shown).

**Digital subtraction angiography**

In the right lobe, tumor stains were recognized along the margin of two large masses, and two hepatic arteries (A5 and A6) were displaced by tumors, which were encased at the margin by a contrast agent (Fig. 3).

**Gallium radioisotope scanning**

In gallium radioisotope scanning, no focus was detected in any organs other than the liver (figure not shown).

**Fig. 1.** A photograph showing abdominal ultrasound.
A massive space-occupying lesion was localized in the right lobe of the liver. The surrounding area was irregular and the inside showed a hypoechoic and heterogeneous pattern.

**Fig. 2.** Photographs showing abdominal dynamic computed tomography.
The margin of a space-occupying lesion was shown by a contrast enhance effect in the arterial phase by a contrast agent (a). However, the contrast enhance disappeared in delayed venous phase (b).
HEPATOCELLULAR CARCINOMA AND SQUAMOUS CELL CARCINOMA

Fig. 3. A photograph showing digital subtraction angiography
In the right robe of the liver, tumor stains were recognized along the margin of two masses, and two hepatic arteries (A5 and A6) were displaced by tumors.

Histology
We performed a fine-needle aspirated liver biopsy under the guide of ultrasound, and obtained tumor tissues (Fig. 4). The tissues were fixed in 3.7% paraformaldehyde and embedded in paraffin. Specimens were sliced at 2 μm, and conventional procedures were performed. A series of specimens were exposed to anti-human involucrin (Biomedical Technologies Inc. Stoughton, MA), anti-epithelial membrane antigen (Immunon Inc. Pittsburgh, PA), anti-cytokeratin No. 19 (Boehringer Mannheim Biochemica, Mannheim, Germany) and anti-keratin (Immunon Inc. Pittsburgh, PA) antibodies. Involucrin is a protein component of the cross-linked envelope synthesized by maturing cells of human stratified squamous epithelia. The pathological diagnosis was poorly squamous cell carcinoma.

Clinical course
After we obtained a histopathological diagnosis of hepatic squamous cell carcinoma, we suspected metastatic cancer of the liver and examined her entire

Fig. 4. Photographs showing histological findings in the liver
a, Hematoxylin eosin staining (×300); b, Immunohistochemical staining using anti-human involucrin antibody (×200); c, Immunohistochemical staining using anti-epithelial membrane antigen (×200); d, Immunohistochemical staining using anti-cytokeratin No. 19 (×200); e, Immunohistochemical staining using anti-keratin (×200) The pathological findings were typical poorly differentiated squamous cell carcinoma.

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body (Table 1). However, we did not find any other primary region. Therefore, we diagnosed the tumor as a primary hepatic squamous cell carcinoma. For therapy, we selected an intra-hepatoarterial chemotherapy because the tumor was located in bilateral hepatic lobes and metastasized in lymphnodes of the hepatic hilus. Ten mg of CDDP and 250 mg of 5-FU per day was continuously injected via a common hepatic artery. Before the treatment, the patient had a constant temperature of 38°C, but the fever improved after 5 days of therapy. The intra-hepatoarterial chemotherapeutic regimen was 3 cycles of CDDP 10 mg and 5-FU 250 mg 5 days per week during admission, and CDDP 10 mg and 5-FU 250 mg 5 days per 2 weeks in the clinic. In December 1998, the tumor in the liver decreased in size, and almost disappeared. However, a recurrence occurred in April 1999, and the patient was re-admitted to our hospital. A chemotherapeutic regimen of CDDP 10 mg and 5-FU 250 mg 5 days per week was performed again. The therapeutic effect of the anti-cancer drugs was weak in the second admission compared to the first. In August 1999, metastasis of the primary cancer was recognized in the spine and lymph nodes in the abdomen. The condition of the patient deteriorated and she died in December 1999.

**DISCUSSION**

In 1975, Barr and Hancock firstly reported a case of a squamous cell carcinoma occurring in association with a primary hepatic cyst completely lined with a stratified squamous epithelium [1]. However, the occurrence of this disease is very rare, and so reports on it are a few [1-11].

Various theories have been advanced concerning the pathogenesis of hepatic squamous cell carcinoma [11]. Chronic inflammation of the bile duct and congenital cysts of the biliary tracts, usually in association with infection and/or stones, have been proposed as etiological factors. Continuous irritation due to chronic infection, followed by metaplastic changes in the biliary epithelium, has been considered to lead to neoplasia. Barr and Hancock [1] and Tomioka et al. [4] suggested that adenosquamous carcinoma arose from squamous metaplasia of adenocarcinoma cells. That is, squamous metaplasia arising from adenocarcinoma cells may have the potential to differentiate into any of a variety of cell types, and hepatic squamous cell carcinoma may occur from adenocarcinoma cells [11]. In addition, there is a theory that hepatic squamous cell carcinoma occurs from hepatocytes or intrahepatic cholangiocytes de novo [6,7], and from the malignant transformation of hepatic
teratoma.

For our patient, we can not explain the pathogenesis of this disease because an autopsy was not performed. However, there was no gallstone, infection or hepatic cyst.

The survival of patients without surgery was less than twelve months. Thus, the prognosis of these patients is poorer than that of patients with the common type of cholangiocellular carcinoma. The survival of 23 months in our patient, who was treated with intra-hepatoarterial chemotherapy using 10 mg of CDDP and 250 mg of 5-FU, is an improvement in cases where surgery is impossible. Nine cases of esophageal cancer with liver metastases treated by intra-hepatoarterial chemotherapy were reported by Maruyama et al. [12]. The intra-hepatoarterial chemotherapy regimen was 1 to 2 cycles of CDDP 20 mg and 5-FU 750 mg for 4 days and subsequent 5-FU 100 mg every week or every other week. As a result, 13% complete remission and 25% partial remission were obtained, and this chemotherapy is suggested to be useful for patients with esophageal cancer with liver metastases. From our report, in patients with primary hepatic squamous cell carcinoma, intra-hepatoarterial chemotherapy with a low dose of CDDP and 5-FU is suggested to be useful and to improve the quality of life.

REFERENCES