Partial Spontaneous Regression of Hepatocellular Carcinoma: A Case with High Concentrations of Serum Lens Culinaris Agglutinin-reactive Alpha Fetoprotein

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Received 15 March 2005, accepted 28 June 2005

Summary: Spontaneous regression of hepatocellular carcinoma (HCC) is rare. There are few reports discussing spontaneous regression associated with serum lens culinaris agglutinin-reactive alpha fetoprotein (AFP-L3). We describe a case of HCC with a high level of AFP-L3, which showed a rapid increase in alpha fetoprotein (AFP) concentration after partial spontaneous regression, and which was then treated successfully. A 71-year-old woman suffering from chronic hepatitis C underwent surgical resection for HCC. Preoperative concentrations of AFP fluctuated; subsequent to a transient decrease, a rapid increase in AFP was observed. AFP-L3 concentration was extremely high. The resected tissue consisted of encapsulated moderately differentiated HCC, subcapsular coagulation necrosis, and chronic active hepatitis. The postoperative course was uneventful. At present, 24 months after diagnosis, no symptoms or signs of tumor recurrence or metastasis have been observed. Although the precise etiology of the spontaneous regression in this patient is not known, we speculate that spontaneous regression of tumor cells with high malignant potential may be related to arterial involvement and insufficient blood supply.

Key words hepatocellular carcinoma, serum lens culinaris agglutinin-reactive AFP (AFP-L3), spontaneous regression

INTRODUCTION

Spontaneous regression of hepatocellular carcinoma (HCC) is rare with only 27 reported cases. The mechanisms underlying spontaneous regression are unknown, but possible schema based on individual histories has been described. There are few reports discussing spontaneous regression associated with serum lens culinaris agglutinin-reactive alpha fetoprotein (AFP-L3). In this report, we describe a case

of HCC with high concentrations of AFP-L3, which showed a rapid increase in alpha fetoprotein (AFP) concentration after partial spontaneous regression, and which was then resected successfully.

CASE REPORT

A 71-year-old woman, who had been suffering from chronic hepatitis C for ten years, was introduced to our hospital for investigation of a liver mass

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Abbreviations: AFP, α -fetoprotein; AFP-L3, serum lens culinaris agglutinin-reactive AFP; CTA, computed tomography during angiography; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MRI, magnetic resonance imaging; PIVKA-II, protein induced by vitamin K absent or antagonist-II; SOL, space-occupying lesion; TAE/TACE, transcatheter arterial embolization/chemo-embolization.

on April 21, 2003. An increased concentration of AFP (1008 ng/ml on April 8, vs. normal, 0 to 20 ng/ml; radioimmunoassay) and a mild elevation of hepatic enzymes were noted by her home doctor. She had no history of alcohol abuse, smoking, blood transfusion, or steroid intake. Physical examination revealed marginal hepatomegaly without ascites, and was otherwise unremarkable. No symptoms of inflammatory disease or gastrointestinal hemorrhage were observed. Laboratory studies showed the following: alanine aminotransferase 64 U/l (normal, 0 to 35 U/l), aspartate aminotransferase 63 U/l (normal, 0 to 35 U/l), platelets 90,000/mm³, total bilirubin 0.5 mg/dl, serum albumin 3.5 g/dl, prothrombin time 79% (12 seconds). HBsAg was negative and antibody to hepatitis C virus was positive. The concentration of tumor markers fluctuated; subsequent to a natural decrease in AFP level, a rapid increase in tumor markers was observed; AFP was 310 ng/ml, AFP-L3 was 90.3% (normal, 0 to 10%; lectin-affinity electrophoresis), and protein induced by vitamin K absence/antagonist-II was 24 mAU/l (PIVKA-II, normal, 0 to 40 mAU/l; electro-chemiluminescence immunoassay), on admission (April 21); these were 3260 ng/ml, 92.4%, and 288 mAU/l, respectively, on May 16. Abdominal computed tomography during angiography (CTA), performed on May 22, showed an encapsulated low density space-occupying lesion (SOL), approximately 3 cm in diameter, in segment 8 of the liver below the diaphragm, and a hyper-enhanced solid mass, approximately 2 cm in diameter, inside and at the edge of the SOL. The capsule was faintly enhanced by contrast; the main feeding artery was A8 with partial support from A4. Abdominal magnetic resonance imaging (MRI) performed on April 24 showed a faint high intensity area in T1WI, which corresponded to the low density area on CTA, a low intensity area with contrast enhancement of the whole tumor in T1WI, and a heterogeneous high intensity area in T2WI, which corresponded to the hyper-enhanced solid mass (Fig. 1). A differential diagnosis between HCC adjacent to a liver cyst with intracystic hemorrhage, HCC with spontaneous necrosis, and cystic carcinoma of the liver was difficult, and we recommended surgical resection. After informed consent, partial hepatic resection and cholecystectomy were performed on June 11. The resected tissue consisted of encapsulated tumor, subcapsular crescent-shaped necrosis, and non-tumorous tissue (Fig. 2). The postoperative course was uneventful. Tumor markers decreased gradually and normalized; AFP, AFP-L3, and

Fig. 1. Imaging studies of the liver. Abdominal CTA showed an encapsulated low density lesion in the liver, and a hyper-enhanced solid mass was detected inside and at the edge of the lesion. The capsule was faintly enhanced by contrast. Abdominal MRI showed a faint high intensity area in T1WI, which corresponded to the low density area on CTA, and a heterogeneous high intensity area in T2WI, which corresponded to the hyper-enhanced solid mass.

Fig. 2. Macroscopic findings of the resected liver. A well demarcated and encapsulated tumor, measuring 3.0 cm in diameter, shows subcapsular crescent-shaped necrosis.

PIVKA-II concentrations were 142 ng/ml, 92.5%, and 16 mAU/l on July 11, and 7.6 ng/ml, undetectable, and 20 mAU/l on September 30, respectively. At present, more than 24 months after detection of the liver mass, no symptoms or signs of tumor recurrence or metastasis have been observed by imaging studies or tumor markers.

(A)

(B)

(C)

Fig. 3. Histological features of the liver tumor (Hematoxylin and eosin stain). (A) The tumor had a fibrous capsule and was composed of necrotic (left) and viable (right) sections (original magnification $\times 20$). (B) The necrotic lesion shows abrupt coagulation necrosis of tumor cells (original magnification $\times 100$). (C) The viable lesion shows proliferation of atypical hepatocytes in a sinusoidal pattern with moderately thickened trabeculae (original magnification $\times 200$).

Histologic findings

Resected tissue was prepared for microscopic examination. The liver tumor, measuring 3.0 cm in diameter, was entirely encapsulated by thin fibrous tissue except for one small focus of capsular invasion. Subcapsular crescent-shaped necrosis on macroscopic examination revealed abrupt coagulation necrosis of tumor cells, occupying about one-third of the tumor volume (Figs 3A, B). The remaining two-thirds of the tumor was viable and showed proliferation of atypical hepatocytes in a moderately thick trabecular pattern with focal solid growth (Fig. 3C). Cytologic atypia of the cancer cells was moderate with a mean mitotic index of 11/10 high power fields. We diagnosed this tumor as moderately differentiated hepatocellular carcinoma. The fibrous capsule at the edge of the necrotic lesion was partly thickened due to granulation tissue with infiltration of chronic inflammatory cells, including hemosiderin-laden macrophages (Figs 4A, B). Furthermore, some obsolescent small arteries were observed within the thickened fibrous capsule by Weigert stain (Fig. 4C). Those features suggested capsular damage or rupture associated with arterial injury prior to surgery; capsular or vascular invasion by cancer cells was not seen in this area.

DISCUSSION

Spontaneous regression of cancer is defined as a partial or complete disappearance of malignancy in the absence of specific treatment [1]. Cases of spontaneous regression published in the English literature are summarized in the Table 1 [2-26]. Although the regression of the tumor in our patient was on a small scale in comparison with other reports, partial spontaneous regression of HCC was confirmed by histologic examination.

The mechanism of spontaneous regression of HCC is unknown. Grossmann et al. [13] categorized spontaneous regression as due to hormonal influences, withdrawal of environmental factors required for tumor growth, selective deprivation of oxygen and nutrients, use of unconventional medicine, and ill-defined immunologic mechanisms altering host resistance. Concrete causes originating in the HCC itself include arterial tumor thrombus and fast tumor growth; exogenous causes include withdrawal from anabolic steroids, abstinence from alcohol, infection, blood transfusion, and gastrointestinal hemorrhage. In our case, no exogenous causes were observed.

(A)

(B)

(C)

Fig. 4. Histology of the thickened capsule of the tumor. (A) Note the protruding lesion of the capsule (star), where inflammatory granulation tissue is observed (Hematoxylin and eosin stain, original magnification $\times 40$). (B) Higher magnification of the lesion of the star in Fig. 4A (original magnification $\times 200$). (C) A collapsed and obsolescent vessel (arrow) is observed within the inflammatory granulation tissue (Weigert stain, original magnification $\times 100$).

Histologic examination showed encapsulated moderately differentiated HCC and subcapsular coagulation necrosis. The preoperative natural decrease in total AFP is explained by this coagulation necrosis. Because part of the viable HCC was not intermingled with the necrotic area, and the margin between those was evident, the cause of necrosis was thought to be a local, rather than a systemic or whole hepatic factor. The regressed area was observed on the periphery of tumor, and was characterized by coagulation necrosis. Although we failed to demonstrate the etiology of the coagulation necrosis directly, the findings within the partly thickened capsule, such as the obsolescent artery and the hemosiderine-laden macrophages, imply a ruptured artery as one cause of the coagulation necrosis.

There are few reports concerning the relationship between spontaneous regression of HCC and AFP-L3. AFP-L3 has served as both a marker for early detection of HCC and a predictive factor for poor survival [27-31]. AFP-L3-positive HCC shows a tendency for early vascular invasion and intrahepatic metastasis. Encapsulation, fibrolamellar polygonal cell types with fibrous stroma, small size, and marked lymphocytic infiltration are associated with a better prognosis, but AFP-L3 seems to be a serologic marker for malignant HCC behavior [32-36]. The AFP-L3 value of the patient before diagnosis was unknown. However, the AFP-L3 concentration tested in our hospital was extremely high. The spontaneous regression may have been caused by tumor cells with high malignant potential invading a feeding artery at an early stage. Subsequent insufficient blood supply may also be associated with expansion of the regression.

It may be remarkable that the preoperative natural decrease in total AFP, which is explained by partial spontaneous regression, was followed by a rapid increase in the AFP level; an increase of over 10-fold in 25 days. The reason for the rapid increase in total AFP level is unclear. Partial necrosis may have stimulated rapid growth in the remnant tumor. Aggressive deterioration of HCC after insufficient transcatheter arterial embolization/chemoembolization (TAE/TACE) is sometimes observed [37]. Increased levels of plasma vascular endothelial growth factor after TACE have been reported [38]. Ischemia may also promote the growth of the remnant tumor, especially in tumors with high malignant potential. Further investigation into the relationship between ischemic change in HCC and tumor growth may be needed.

TABLE 1.
Characteristics of spontaneous regression of hepatocellular carcinoma

Authors [reference no.]	Related hepatitis virus	Tumor size (cm)	Alpha-fetoprotein (ng/ml)/normalized	Disappearance	Proposed mechanism	Remarks
Johnson et al. [2]	Unknown	6	Unknown/Yes	Partial*	Withdrawal from anabolic steroid	Septicaemia
Gottfried et al. [3]	B	Multifocal	Normal	Complete*	Unknown	Abstinence from alcohol
Lam et al. [4]	B	Unknown (+ Lung metastasis)	Unknown	Complete*	Unknown	Infection of the tumor
Sato et al. [5]	B	10 (+ Bone metastasis)	23000/Yes	Complete*	Unknown	Herbal medicine
Suzuki et al. [6]	non-B	3.2	7767/Yes	Complete*	Due to rapid growth	No
Tocci et al. [7]	non-B	5	625/Yes	Complete*	High sensitivity to reduction of blood supply	Gastrointestinal bleeding
Gaffey et al. [8]	non-B	10	2690/Yes	Complete***	Unknown	Macrobiotic diet Gastrointestinal bleeding with ascites
Ayres et al. [9]	non-B	Multifocal (+ Lung metastasis)	7390/Yes	Partial*	Unknown	No
Chien et al. [10]	B	12	>10000/Yes	Complete*	Unknown	Herbal medicine
Imaoka et al. [11]	C	Unknown	6609/Yes	Partial**	Due to arterial thrombus	No
McDermott et al. [12]	Unknown	15	Unknown	Complete*	Unknown	No
Grossmann et al. [13]	non-B, non-C	4.5	310/Yes	Partial*	Unknown	Abstinence from alcohol Silymarin, Gastric cancer
Ozeki et al. [14]	Unknown	5	1050/Yes	Complete**	Unknown	No
Markovic et al. [15]	B	13	11/Unknown	Complete**	Due to excessive cytokine	No
Van Halteren et al. [16]	non-B, non-C	8	Unknown	Partial*	Due to poor vasculature in cirrhotic liver	No
Iwasaki et al. [17]	C	3.8	105340/Yes	Partial*	Due to rapid growth	No
Sanz et al. [18]	C	10 (+ Bone metastasis)	4/Yes	Complete*	Unknown	S-adenosyl L- methionine
Kacynski et al. [19]	Unknown	7	Unknown	Complete*	Unknown	No
Ohba et al. [20]	C	>5	429998/Yes	Partial*	Due to absopal effect of irradiation (TNF- α)	Radiotherapy for bone metastasis
Magalotti et al. [21]	non-B	1-3	2500/Yes	Complete*	Unknown	HCC recurred 4 years later
Magalotti et al. [21]	B, C	1.5-4.5	37500/No	Partial*	Unknown	HCC recurred 17 months later
Stoelben et al. [22]	non-B, non-C	6	Normal	Partial**	Unknown	Liver abscess-like symptom
Stoelben et al. [22]	B	7	3850/Yes	Partial**	Unknown	Liver abscess-like symptom
Takeda et al. [23]	C	6.3 Multifocal	8230/Yes	Complete*	Unknown	Herbal medicine HCC recurred 17 months later
Uenishi et al. [24]	C	12	4796/Yes	Partial**	Due to portal vein tumor thrombi	No
Matsuo et al. [25]	C	3.5	1000/Yes	Complete**	Due to ischemia or immune response	No
Nakai et al. [26]	C	3 Multifocal	Normal	Complete*	Due to immune response (NK cell)	No
Present case	C	3	3260/Yes	Partial**	Due to rupture of artery	High concentration of AFP-L3

*: Diagnosed by imaging study **: Diagnosed by surgical resection ***: Diagnosed by autopsy

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