CASE REPORT

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Spontaneous regression of recurrent hepatocellular carcinoma after TAE: possible mechanisms of immune mediation

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Abstract We report findings in a 76-year-old man who underwent a lateral segmentectomy of the liver for hepatocellular carcinoma in July 1996. In July 1997, transarterial embolization (TAE) was performed for recurrent tumors in the remnant liver. Augmentation of the tumors and an increase in protein induced by vitamin K absence or antagonist (PIVKA)-II level were noted in October 1997, and, although we recommended TAE again, the patient and his family refused further treatment. Subsequently, the patient was only observed, and, except for a small lesion that was probably a scar, no tumors were noted on image examinations in November 1998, and the PIVKA-II level had returned to a normal value at this time. Two years after the regression, the tumors appeared to be in complete spontaneous remission. This patient had no history indicative of ischemic necrosis, and levels of cellular surface markers for natural killer (NK) cells and NK cell activity showed high values, which suggested that tumor immunity was activated by some, unknown, mechanism.

Key words Spontaneous regression · Hepatocellular carcinoma · Tumor immunity · Natural killer cell activity

Introduction

Spontaneous regression of a malignant tumor is extremely rare, particularly in hepatocellular carcinoma (HCC). Although immunological mechanisms may play important roles in spontaneous regression, to our knowledge, there have been no reports of detailed investigations of such phenomena. In this report, we describe a patient with spontaneous regression of recurrent HCC and report the immunological findings, which, we speculated, were the possible cause of the spontaneous regression.

Case report

The clinical course of the patient, a 76-year-old man with liver cirrhosis caused by the hepatitis C virus, is shown in Fig. 1. In July 1996, he underwent a relatively curable operation, involving lateral segmentectomy of the liver, for HCC, classified as stage III (T3N0M0) according to the TNM classification of the Liver Cancer Study Group of Japan. The histological findings showed moderately differentiated HCC with a trabecular pattern. In July 1997, transarterial embolization (TAE) was performed for multiple recurrent tumors in the remnant liver. In October 1997, the tumors showed augmentation, and the level of protein induced by vitamin K absence or antagonist-II (PIVKA-II), as determined by an immunoradiometric assay, was elevated, at 675 mAU/ml (normal range, 0–40 mAU/ml). At this time, the level of alpha-fetoprotein (AFP), shown by radioimmunoassay, was slightly elevated, but within the normal range (0–20 ng/ml).

On October 23, 1997, abdominal computed tomography (CT) showed multiple tumors, approximately 3 cm in diameter, in S1, S4, and S5 of the liver (Fig. 2). Although we recommended TAE again, the patient and his family refused further treatment, and subsequently we only observed the patient. During the next 12 months, no cancer treatment was administered and no blood chemistry and imaging examinations were performed. On abdominal CT in October 1998 (Fig. 3), no tumors were noted, except for a small lesion that was probably a scar, and the PIVKA-II level, at 17 mAU/ml, had decreased to within the normal range (Fig. 1). Two years after the regression, no tumors were detectable by image examinations, and the tumor marker levels had remained within normal limits.

Immunological test findings after the spontaneous regression, in November 1998, and September 2000, are...
shown in Table 1. Levels of IgG, IgA, IgM, C3, and C4 were estimated via immunonephelometry. Antinuclear antibodies were determined by the indirect immunofluorescence method. The latex method was used for the lupus erythematosus test. Cellular surface markers were determined by flow cytometry, and lymphocyte blast transformation was determined by the 3H-thymidine uptake test. Natural killer (NK) cell activity was measured using the 51Cr-release method (target cell, K562; effector cell/target cell ratio, 20:1). In November 1998, serum values of examined items were normal, except that IgG and IgA levels were high, at 2220 mg/dl and 1310 mg/dl, respectively. NK cell activity was slightly elevated, at 55%. In the analysis of cellular surface markers, CD16, CD56, and CD57 showed high levels of NK cells, at 38.7%, 48.1%, and 44.6%, respectively, whereas other markers were normal. In September 2000, the findings for cellular surface markers were similar to the findings in November 1998.

Table 1. Immunological test findings

| November 1998 | Serum examination | IgG, 2220 mg/dl (1000–2060 mg/dl); IgA, 1310 mg/dl (115–440 mg/dl); IgM, 74 mg/dl (74–330 mg/dl); C3, 60 mg/dl (50–109 mg/dl); C4, 12 mg/dl (11–47 mg/dl); antinuclear antibody, 40-fold (–); lupus erythematosus test (–)
| Cellular surface markers | CD3, 51.2% (58.6–89.0%); CD4, 32.7% (30.5–53.7%); CD8, 24.5% (17.4–43.0%); CD4/CD8, 1.3 (0.5–2.3); CD16, 38.7% (1.5–25.5%); CD20, 6.2% (4.1–22.1%); CD56, 48.1% (3.8–28.6%); CD57, 44.6% (3.9–23.5%)
| Cellular immunity | NK cell activity, 55% (18–40%)
| Lymphocyte blast transformation test (PHA stimulation index) | 211.7 (74–508)

| September 2000 | Cellular surface markers | CD3, 52.9%; CD4, 34.1%; CD8, 21.1%; CD4/CD8, 1.6; CD16, 39.0%; CD20, 8.0%; CD56, 42.6%; CD57, 39.1%

Figures in parentheses show normal ranges
PHA, Phytohemagglutinin; NK, natural killer

Discussion

Spontaneous regression of a neoplasm is defined as the partial or complete disappearance of a malignant tumor mass without any treatment, or as a result of therapy that is considered inadequate to influence a systemic neoplastic disease, and it has been estimated to occur in one of 60000 to 100000 patients with a malignant disease. The greatest numbers of such spontaneous regressions are reported in patients with neuroblastomas, renal cell carcinomas, malignant melanomas, and lymphomas/leukemias, and the spontaneous regression of a primary malignant liver tumor is rare.

Mechanisms that have been proposed for spontaneous regression of human cancer include immune mediation, tumor inhibition by growth factors and/or cytokines, induction of differentiation, hormonal mediation, elimination of a carcinogen, tumor necrosis, and/or angiogenesis inhibition, psychological factors, apoptosis, and epigenetic mechanisms. However, the phenomenon remains to be elucidated.

Nineteen cases of spontaneous HCC regression have been reported in the English-language literature, and it is speculated that necrosis, caused by an ischemic disorder, and tumor immune activation are important causal factors. When we evaluated the causes of spontaneous regression in the 19 patients reported, 5 involved necrosis, and 8 involved immunity. Because not only the primary focus but also the metastatic lesions regressed in 2 patients, this phenomenon cannot be explained by ischemic effects. In such instances, immunological mechanisms may play an important role in spontaneous regression. As a probable mechanism of spontaneous