

CASE REPORT

Abscopal regression of hepatocellular carcinoma after radiotherapy for bone metastasis

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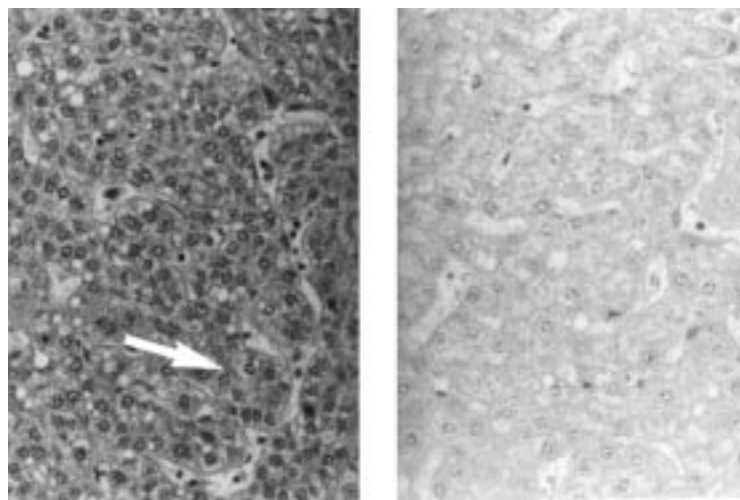


Figure 1 Histological examination of a section of the tumour of the liver showing a well differentiated hepatocellular carcinoma (left panel). Note the rather slender cell cord composed of small tumour cells. Microacinar formation (arrow) is also seen. Nuclear crowding is evident compared with that in control tissue obtained from the same liver (right panel). Haematoxylin and eosin; original magnification $\times 80$.

Abstract

Spontaneous regression of hepatocellular carcinoma is a rare phenomenon. Abscopal regression of tumours resulting from the effect of irradiation of a tissue on a remote non-irradiated tissue is also rare. The case of a 76 year old Japanese man with hepatocellular carcinoma that regressed after radiotherapy for thoracic vertebral bone metastasis is described. Serum levels of tumour necrosis factor- α increased after radiotherapy. The findings suggests that such abscopal related regression may be associated with host immune response, involving cytokines such as tumour necrosis factor- α .

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Keywords: hepatocellular carcinoma; abscopal effect; radiotherapy; tumour necrosis factor- α ; bone metastasis; spontaneous regression

Hepatocellular carcinoma (HCC) is one of the most common malignancies in the world, the incidence being particularly high in South Africa and Asia.¹ Although early detection of tumours and introduction of new therapies is likely to improve prognosis, non-resectable and



Figure 2 Hepatic angiogram obtained in November 1992 showing multiple hypervascular stains in the right lobe (arrows).

advanced stage HCCs have a very poor prognosis.² However, several reports have described spontaneous regression of malignant diseases including HCC,³⁻¹⁶ with a frequency of no more than 1 in 60 000 to 100 000 patients with cancer.³ The term "abscopal" was first used by Mole¹⁷ to denote the effect that irradiation of a tissue has on a remote non-irradiated tissue in the same subject. Such an effect has been described in various tumours,^{18 19} but abscopal regression of HCC is extremely rare. We describe the case of a patient who presented with HCC that regressed after radiotherapy for thoracic vertebral bone metastasis. The regression of the liver tumour probably represents an abscopal effect of irradiation. In this patient, we determined serum concentrations of interleukin (IL)-1 β , IL-2, IL-4, IL-6, hepatocyte growth factor (HGF), and tumour necrosis factor (TNF)- α before and after radiotherapy.

Case report

A 76 year old Japanese man was admitted to our hospital in May 1995 complaining of severe back pain. In 1990, he was diagnosed with HCC associated with antibody to hepatitis C virus positive liver cirrhosis, and underwent partial resection of the liver. Histological examination showed a well differentiated



Figure 3 Thoracic and abdominal computed tomography scans obtained in June 1995 showing a mass in the second thoracic vertebra (arrow) (A) and multiple low densities in the liver (arrowheads) (B).

HCC²⁰ in S5 of the liver, measuring 1.5 cm in diameter (fig 1). In November 1992, recurrence of the HCC was diagnosed on the basis of the presence of multiple hypervascular tumours on hepatic arteriography (fig 2). The patient was treated with five courses of transcatheter arterial embolisation performed with gelatin sponge (Gelfoam; Pharmacia & Upjohn, Kalamazoo, Michigan, USA) and/or hepatic arterial infusion chemotherapy using mitomycin (total cumulative dose 50 mg), epirubicin (total cumulative dose 46 mg), or doxorubicin (total cumulative dose 41 mg) and two courses of percutaneous ethanol injection during the period between November 1992 and November 1994. However, multiple HCCs were persistently detected in the liver, together with a gradual increase in serum α fetoprotein (AFP). The patient had not received any blood transfusions during this period and was not on any herbal medicine.

On admission, physical examination showed hypoesthesia of the lower extremities and hepatomegaly (5 cm below the costal margin). Laboratory tests gave the following results: haemoglobin, 13.8 g/dl; leucocyte count, 3700/mm³; platelet count, 140 000/mm³; total bilirubin, 2.2 mg/dl; aspartate aminotransferase, 111 IU/l; alanine aminotransferase, 38 IU/l; albumin, 3.2 g/dl; alkaline phosphatase, 349 IU/l; AFP, 429 998 ng/ml (normal range <20 ng/ml); and a protein induced by vitamin K absence or antagonist-II (PIVKA-II), 4.9 AU/ml (normal range <0.1 AU/ml). A thoracic computed tomography (CT) scan at that stage showed a mass in the second thoracic vertebra (fig 3A), and scintigraphy showed uptake of radionuclide in the same lesion. An abdominal CT scan showed cirrhosis of the liver with multiple low density masses (fig 3B). A

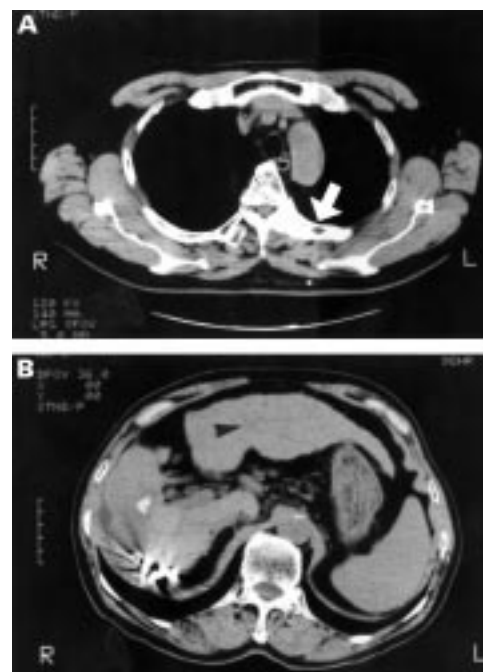


Figure 4 Thoracic and abdominal computed tomography scans showing disappearance of the mass from the second thoracic vertebra (arrow) (A) and a remarkable regression of the hepatic lesions (arrowhead) (B) one month and 10 months after radiotherapy respectively.

diagnosis of HCC with bone metastasis prompted radiotherapy of the bone lesion with a total dose of 36 Gy. This treatment produced immediate relief of back pain, and thoracic CT performed one month after radiotherapy showed the disappearance of the mass from the second thoracic vertebra (fig 4A).

Serum levels of AFP and PIVKA-II decreased to 10 ng/ml and <0.1 AU/ml respectively, without systemic chemotherapy during or after radiotherapy (fig 5). Moreover, abdominal CT performed 10 months later showed remarkable regression of the hepatic lesions to very small masses (fig 4B). Serial measurements of serum concentrations of IL-1 β , IL-2, IL-4, IL-6, HGF, and TNF- α before and after radiotherapy were retrospectively performed using sera stored at -80°C. The serum level of TNF- α began to increase 7 months before radiotherapy, reaching 102 pg/ml after therapy. The patient remains well, and his serum levels of AFP and PIVKA-II were still between 10 and 100 ng/ml and within the normal range respectively at the latest follow up in October 1997.

Discussion

Although no histological evidence of recurrent HCC was available in our patient, the results of several tests, including the presence of a well differentiated HCC on initial diagnosis, characteristic hypervascular stains on an hepatic angiogram, and extremely high levels of AFP, strongly suggested recurrent HCC with metastasis to the thoracic vertebra. Although it is possible that the high levels of AFP were partially due to the treatment of the thoracic metastasis, the dramatic response to radiotherapy, including the disappearance of the

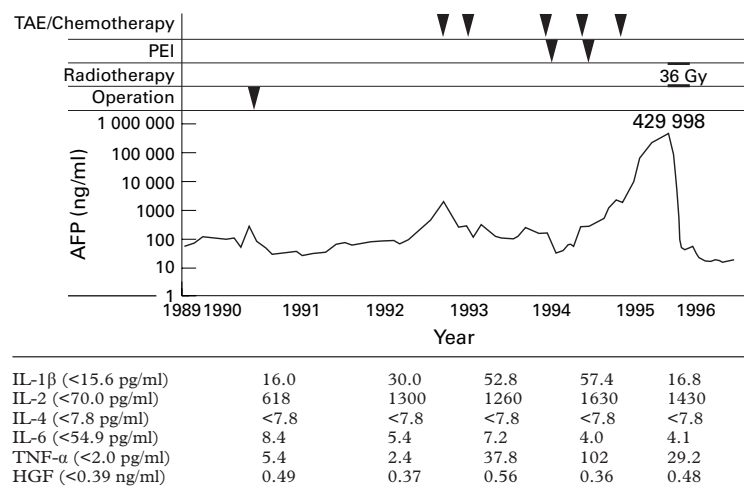


Figure 5 Clinical course. Note the immediate fall in serum a fetoprotein (AFP) and increase in tumour necrosis factor (TNF)-α after radiotherapy for bone metastasis. TAE, transcatheter arterial embolisation; PEI, percutaneous ethanol injection; HGF, hepatocyte growth factor.

vertebral lesion and a marked fall in AFP levels, adds support to our diagnosis. More importantly, abdominal CT showed a dramatic regression of the hepatic lesions, although this regression was not confirmed by angiography or isotope scan.

Spontaneous regression of tumours has been reported in a variety of malignant diseases including HCC.³⁻¹⁶ The mechanisms of spontaneous regression of HCC are still obscure, although various factors have been discussed in previous reports, such as high fever,⁴ alcohol withdrawal,⁵ haemorrhagic shock and tumour anoxia,^{6,7} hepatic artery occlusion,⁸ surgery with blood transfusion,⁹ and treatment with herbal medicine.^{10,11} It has also been suggested that immunological mechanisms may play an important role in this rare phenomenon.^{3,4}

Interestingly, our case is similar to that reported by Mochizuki *et al*¹² as both patients were Japanese men with high levels of AFP and regression occurred after radiotherapy to bone metastasis. An abscopal effect has been described for various tumours,^{18,19} but no reports of abscopal regression of HCC precede the description of Mochizuki *et al*¹² and the present case. The possible effects of irradiation scattered beyond the treatment volume including the liver must be considered. However, the dose of the scattered irradiation to the liver in these two cases was unlikely to be therapeutically effective for HCC. An alternative mechanism of this effect may include the release of antigen following tumour lysis, reduction of immunosuppressive tumour bulk, suppression of radiosensitive immune suppressor mechanisms, and activation of host immune responses.¹⁹ To provide further evidence for the

above mechanisms, we retrospectively measured serial changes in a variety of cytokines. Serum levels of TNF-α increased after radiotherapy, but the levels of the other cytokines measured did not change. TNF-α is known to enhance the cytolytic activity of natural killer cells and may mediate tumour regression through this mechanism, although clinical administration of this cytokine fails to produce a significant therapeutic effect.²¹ Therefore, in our case, the abscopal regression of HCC may be associated with high levels of TNF-α production.

To our knowledge, this is the first report in which serum levels of cytokines were serially measured in a case of abscopal regression of HCC following radiotherapy. Although the clinical significance of these cytokines has not been fully assessed, accumulation of similar data should enhance our understanding of this extremely rare phenomenon.

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