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CASE REPORT

Spontaneous Regression of Hepatocellular Carcinoma: Three Case Reports and a Categorized Review of the Literature

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Introduction

Hepatocellular carcinoma (HCC) is the most frequent form of primary liver cancer and the fifth most prevalent cancer worldwide [1]. Spontaneous tumor regression was first defined by Cole and Everson [2] as complete or partial clearance of malignant cells in the absence of any specific treatment, particularly antineoplastic chemotherapy. However, it may also occur during or after therapy, a situation in which therapy could be endorsed with an undeserved antitumor effect. Spontaneous tumor regression was at first thought to be an extremely infrequent phenomenon, with an estimated incidence of 1 in 60,000–100,000 cases [3]. Its mechanism is largely unknown, however, it has important implications in clinical research and clinical practice. The number of cases of spontaneous regression reported in the literature is higher in HCC than in other neoplasms [4], possibly reflecting a higher incidence. However, due to its exceedingly low frequency it would probably not affect the results of any study on HCC therapy. Following our observation of two cases of spontaneous regression and one case of sustained, complete regression in the course of a chemotherapeutic regimen with marginal efficacy in the treatment of this tumor, we have searched the cases published in the English literature and reviewed the possible mechanisms involved in such remarkable events.

We have retrospectively reviewed all the cases recorded in our liver unit in which an objective tumor remission was observed that could not be convincingly ascribed to a therapeutic effect of any rational intervention. These consist of tumor ablation, any sort of embolizing procedure performed in the hepatic artery or its branches (including intra-arterial injection of Lipiodol for diagnostic or staging purposes), or pharmacological therapy that might have a known antiproliferative effect. Medical records of these patients were thoroughly reviewed trying to find any possible event that may have triggered the observed remission.

Clinical Observations

Two patients were identified that seemingly had had spontaneous regression of their HCC during follow-up in our liver unit. One other patient with a complete response that was hardly explainable based only on the chemotherapeutic treatment received is also described.

Case 1

A 54-year-old male had a diagnosis of hepatitis B virus-related liver cirrhosis with complete portal vein thrombosis in 1989. Starting in 1997 a steady but slow increase in alpha-fetoprotein (AFP) was observed (Fig. 1). In February 1998

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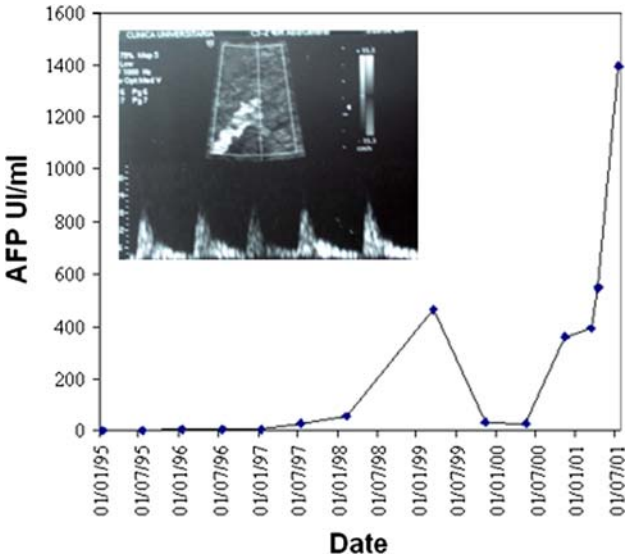

Fig. 1 Regression in patient 1. Arterial blood flow within the portal vein thrombus (**a**) and changes in serum AFP during follow-up

computed tomography (CT) revealed no focal lesions but after intra-arterial Lipiodol injection a 15-mm lesion in segment VI was detected on CT. Fine-needle aspiration biopsy revealed normal hepatocytes with fat changes. This lesion progressively grew thereafter to reach 30 mm in September 1998. In March 1999, arterial blood flow was observed by Doppler ultrasonography (US) inside the portal thrombus adjacent to this ill-defined lesion. Serum AFP at that time was 465 UI/ml. At the next follow-up (November 1999) the lesion measured 16 mm and serum AFP had dropped to 33 UI/ml. No lesion was detected on CT performed on May 2000 when AFP was 27 UI/ml. One year later AFP had peaked at 550 UI/ml and two new lesions that measured 9 and 8 mm, respectively, were detected on segments II and VI, respectively. Thereafter, AFP increased progressively to 20,990 UI/ml at the time when the patient died in March 2002. This patient received no pharmacological treatment that might have negatively influenced tumor growth and no mechanism of tumor regression was suggested by his medical history.

Case 2

A 61-year-old male had a diagnosis of alcoholic liver cirrhosis with portal hypertension thrombosis in April 2002. Routine ultrasound on November 2003 detected a focal hypervascular lesion with a diameter of 35 mm on the right lobe (Fig. 2). Typical features of HCC after contrast injection were also found on a magnetic resonance imaging (MRI) scan and the patient was successfully evaluated for liver transplantation. Transarterial embolization with Embospheres^{TM} was performed on December 2003 but not repeated because of incomplete response on CT scan evaluation 6 weeks later. Tumor was stable on July 2004 but showed clear progression towards segment I in October 2004. Serum AFP had increased from 7 UI/ml in July 2004 to 3,977 UI/ml in September 2004 and to 27,353 UI/ml in October 2004. In March 2005, MRI showed partial remission in volume of the tumor lesion that was entirely avascular, and AFP had dropped to 6 UI/ml. In July 2005, CT scan showed complete remission and normal AFP. On September 2005 a new hypervascular lesion of 18 mm was detected by CT at a different location that has grown steadily and measured 30 mm in January 2007. AFP remains normal.

Although this patient had been treated intra-arterially it is extremely unlikely that the single session of transarterial embolization procedure performed more than 1 year before remission could be the mechanism of tumor regression in this case. Rapid tumor growth could be invoked when considering that AFP peaked from 3,977 to 27,353 UI/ml in 30 days immediately before remission.

Case 3

A 60-year-old male was diagnosed of familiar hemochromatosis in 2000. In September 2003 increased levels of AFP (66 UI/ml) were found on routine follow-up and CT and MRI showed a mass in the right lobe of the liver that invaded the main portal vein and had typical imaging features of HCC (Fig. 3). Enlarged lymph nodes were also observed in the celiac axis. In February 2004 he started treatment with oxaliplatin and gemcitabine. At that time AFP was 44 UI/ml. In May 2004, no response was observed after four courses of therapy, AFP was 6,865 UI/ml, and the main tumor mass measured 110 mm. Two more courses were then administered before stopping chemotherapy in July 2004. One month later, MRI scan showed a clear, nonmeasurable volume regression of the tumoral thrombus that was confirmed in October 2004 when a new MRI scan failed to show any distinct focal liver lesion and AFP was 1.55 UI/ml. In October 2006, MRI still showed complete remission and AFP was 1.62 UI/ml. Three years after diagnosis the patient is still in complete remission.

This patient had received antineoplastic chemotherapy but several reasons make it extremely unlikely that tumor response was in fact a delayed response to chemotherapy. Firstly, it occurred after objective tumor progression early during therapy. Secondly, the combination of oxaliplatin and gemcitabine has only marginal effect in inducing tumor regression in HCC patients [5–7]. Thirdly, the sustained nature of this regression (more than 3 years) is beyond what can be expected from chemotherapy-induced tumor remission.

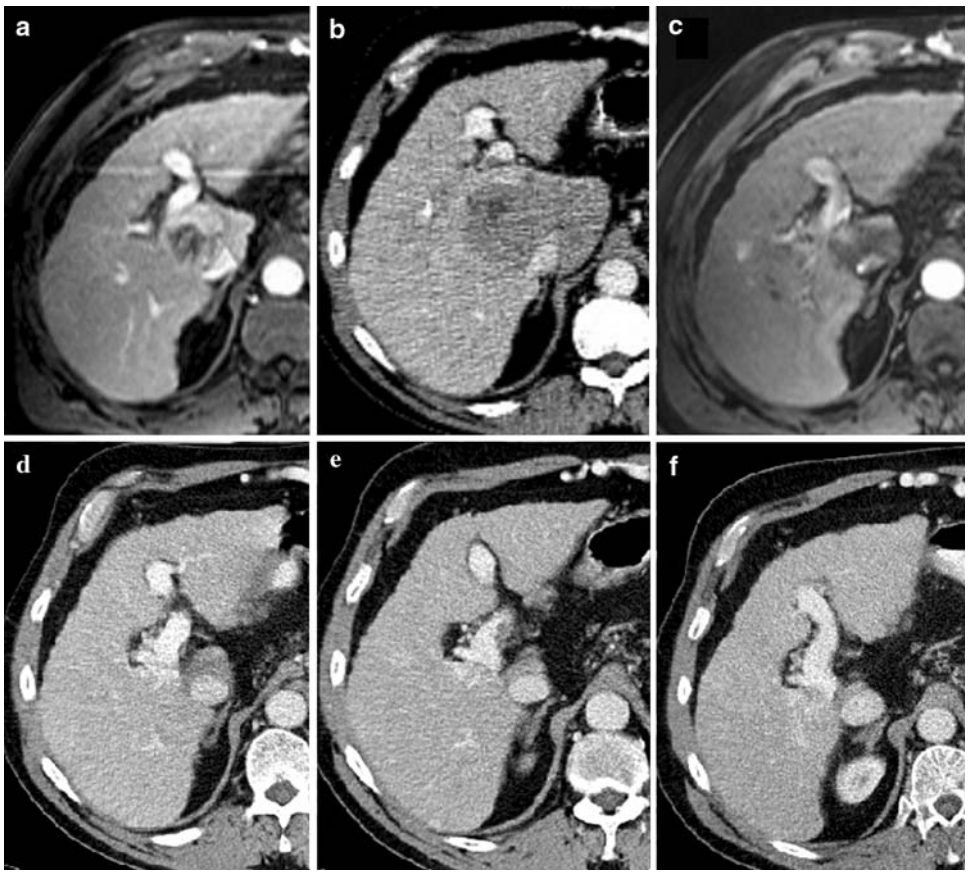

Fig. 2 Regression in patient 2. Imaging procedures correspond to the following dates: (**a**) October 2004, (**b**) December 2004, (**c**) March 2005, (**d**) July 2005, (**e**) September 2005, and (**f**) December 2006

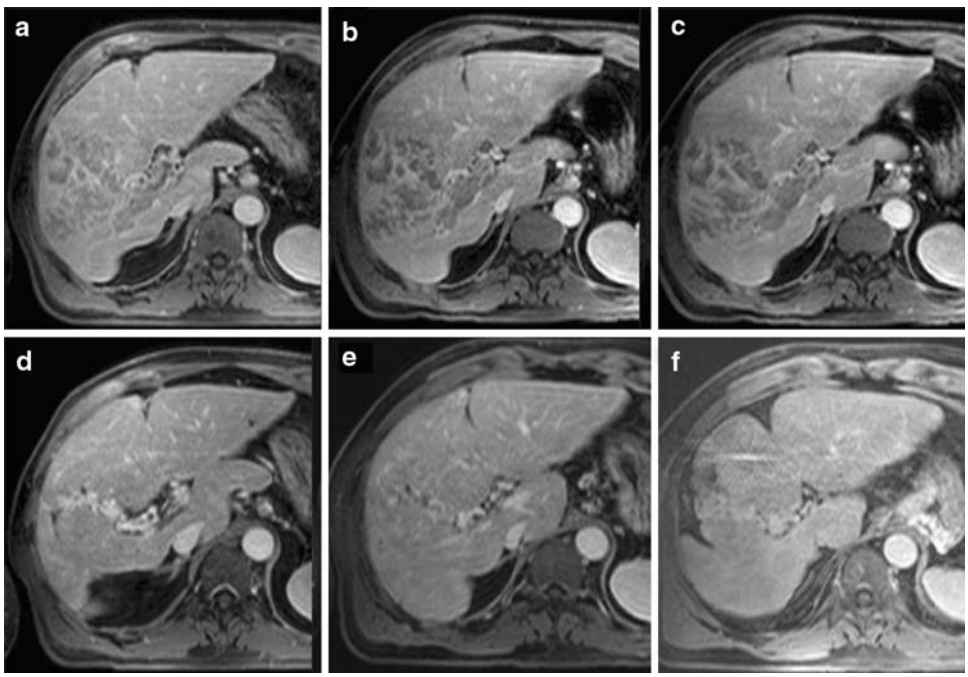

Fig. 3 Regression in patient 3. Imaging procedures correspond to the following dates: (**a**) February 2004, (**b**) March 2004, (**c**) May 2004, (**d**) July 2004, (**e**) October 2004, and (**f**) October 2006

Discussion

The nature and possible pathogenic mechanism of previous reports on spontaneous regression of HCC was reviewed among 65 reports of partial and complete spontaneous regression of HCC that have been published. Two reports published in a Korean journal were excluded due to lack of access to the full paper. Six cases were excluded because

Table 1 Summary of published case reports of spontaneous regression of HCC and proposed mechanisms

References	Year	Histology pre	Histology post	Change in volume	Reduced vascularization	Change in AFP	Possible cause
Radiological complete remission (positive previous diagnosis)							
[20]	2001	Pos	NA	Disappearance	Yes	NE	Unknown
[53]	1985	Pos	NA	Disappearance	NA	NE	Androgen withdrawal
[47]	1990	Pos	NA	Disappearance	NA	Decrease	Ischemia
[34]	1998	Pos	NA	Disappearance	NA	Decrease	Unknown
[36]	1998	Pos	NA	Disappearance	NA	NE	NSAIDS
[15]	2004	Pos	NA	Disappearance	NA	Decrease	Herbal
[52]	1985	Pos	NA	Disappearance	Yes	Decrease	Ischemia
[45]	1992	Pos	NA	Disappearance	Yes	Decrease	Herbal
[43]	1994	Pos	NA	Disappearance	Yes	NA	Unknown
[25]	2000	Pos	NA	Disappearance	Yes	Decrease	Herbal
[24]	2000	Pos	NA	Disappearance	Yes	Decrease	Unknown
[27]	2000	Pos	NA	Disappearance	NA	Normal	Unknown
[11]	2004	Pos	NA	Disappearance	Yes	Normal	Unknown
[12]	2004	NA	NA	Disappearance	Yes	Decrease	Antidiabetics
[50]	1989	NA	NA	Disappearance	Yes	Decrease	Rapid growth
[57]	2001	NA	NA	Disappearance	NA	Decrease	Unknown
[41]	1996	NA	NA	Disappearance	NA	Decrease	Unknown
Radiological partial remission (positive previous diagnosis)							
[53]	1985	Pos	NA	Reduction	NA	NE	Androgen withdrawal
[48]	1990	Pos	NA	Reduction	NA	Decrease	Ischemia
[49]	1990	Pos	NA	Reduction	NA	Decrease	Unknown
[37]	1997	Pos	NA	Reduction	NA	NE	Unknown
[33]	1998	Pos	NA	Reduction	NA	Decrease	Unknown
[34]	1998	Pos	NA	Reduction	NA	Decrease	Unknown
[29]	2000	Pos	NA	Reduction	NA	Decrease	Ischemia
[9]	2005	Pos	NA	Reduction	NA	Decrease	Bystander effect
[38]	1997	Pos	NA	Reduction	No	Decrease	Rapid growth
[10]	2004	Pos	NA	Reduction	No	NE	Rapid growth
[58]	2007	Pos	NA	Reduction	NA	Normal	Bystander effect
[59]	2007	Pos	NA	Reduction	NA	Decrease	Unknown
[13]	2004	NA	NA	Reduction	NA	Decrease	Ischemia
[26]	2000	NA	NA	Reduction	No	Decrease	Abstinence from alcohol
[26]	2000	NA	NA	Reduction	Yes	Decrease	Ischemia
[14]	2004	NA	NA	Reduction	Yes	Decrease	Ischemia
[60]	2005	NA	NA	Reduction	Yes	Decrease	Vitamin K
[61]	2005	NA	NA	Reduction	Yes	Normal	Unknown
[22]	2001	NA	NA	Reduction	NA	Decrease	Unknown
Histologically proven complete remission							
[55]	1982	Pos	Neg	Disappearance	NA	Normal	Abstinence from alcohol
[54]	1982	Pos	Neg	Disappearance	NA	NA	Herbal
[35]	1998	Pos	Neg	Disappearance	NA	NA	Unknown
[40]	1996	Pos	Neg	Reduction	NA	NE	Infection
[42]	1995	Pos	Neg	Reduction	No	Decrease	Abstinence from alcohol
[31]	1999	NA	Neg	Disappearance	Yes	Decrease	Unknown
[21]	2001	NA	Neg	Reduction	NA	Decrease	Unknown
[17]	2003	NA	Neg	Reduction	No	Decrease	Unknown
[8]	2005	NA	Neg	Reduction	Yes	NE	Infection

Table 1 continued

References	Year	Histology pre	Histology post	Change in volume	Reduced vascularization	Change in AFP	Possible cause
[39]	1996	NA	Neg	NA	NA	Decrease	Unknown
[28]	2000	NA	Neg	NA	NA	NE	Unknown
[16]	2003	NA	Neg	NA	NA	NE	Unknown
Histologically proven partial remission							
[18]	2002	NA	Pos	NA	NA	Decrease	Ischemia
[44]	1994	NA	Pos	NA	No	Decrease	Ischemia
[32]	1998	NA	Pos	Reduction	NA	Decrease	Infection
[46]	1991	NA	Pos	Reduction	NA	Decrease	Bystander effect
[23]	2000	NA	Pos	Reduction	NA	Decrease	Rapid growth
[14]	2004	NA	Pos	Reduction	Yes	Decrease	Ischemia
[62]	2007	NA	Pos	Reduction	NA	Decrease	Unknown
[63]	2005	NA	Pos	Reduction	Yes	Decrease	Unknown
Biochemical remission							
[19]	2002				NA	Decrease	Unknown
[19]	2002				NA	Decrease	Unknown
[19]	2002				NA	Decrease	Unknown

NE, not evaluable (only one value); NA, not available; Pos, positive; Neg, negative

the diagnosis of HCC was not unequivocal, leaving 59 reports available for analysis.

Table 1 [8–56] summarizes the 59 clinical reports of spontaneous regression of HCC. Clinical profile and demographics vary widely. Tumor regression, either partial or complete, has been reported in patients with single and multiple lesions, with and without extrahepatic metastases, and with our without having received prior ineffective antineoplastic therapies. Regarding the possible pathogenic mechanism underlying tumor regression, no possible cause was detected in 27 out of 59 cases (46%). Among the remaining 32 patients, ischemia due to hemorrhagic shock or hepatic artery thrombosis was identified in 10 patients (31%). Rapid tumor growth, which may result in relative tumor ischemia, heralded tumor regression in another four patients (13.0%). On the other hand, a distant bystander effect was recorded in six patients (18%) in which events able to trigger an immune response occurred before remission. External irradiation of extrahepatic metastasis (brain and bone), bland embolization of the primary liver tumor, and a distant infection were identified in two, one, and three patients, respectively. Interestingly, three patients (9%) had stopped alcohol consumption in the previous months. And finally, current or previous drug therapies with no established antiproliferative effect were recorded in nine patients (28%), including oral antidiabetics, vitamin K, nonsteroidal anti-inflammatory drugs (NSAIDs), herbal remedies, and androgens.

What lies behind spontaneous tumour regression? Lin et al. [11] proposed four different categories, including ischemia and immune response. Ischemia can produce necrosis of an oxygen-sensitive malignancy, and it may result from rapid tumor growth [50], arterioportal shunt [31], disturbance in hepatic circulation associated with portal vein thrombosis [23], poor arterial supply in cirrhotic liver [37], arterial thrombosis [44], hemorrhagic shock due to massive gastrointestinal [48] or peritoneal bleeding [14], or iatrogenic subintimal injury during hepatic angiography [51]. This vascular hypothesis is likely to be highly relevant since both in the reviewed literature and in our own experience presented herein patients usually have portal thrombosis, and any invasion of an arterial branch within the tumor, which is highly oxygen support dependent, may in fact induce tumor regression. An immunological mechanism involving intense cytokine production may be triggered by any tumor treatment that, although intrinsically inefficacious, may help eliciting an immune response (e.g., after favoring antigen presentation, as may occur after palliative irradiation of a bone metastases [33]), or by any event that may cause nonspecific immunopotentiation, such as a reaction to a distant bacterial infection [32]. Spontaneous tumor regression is by and large a medical enigma in most cases. Unfortunately, when spontaneous regression occurs in the setting of nonmedical therapeutic interventions it can result in ascribing miraculous properties to products that lack intrinsic activity.

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