

Late Extrahepatic Recurrence of Hepatocellular Carcinoma after Liver Transplantation: A Rare Case Report and Literature Review

Riccardo Solimando, Gian Maria Prati, Patrizia Perazzo, Giuseppe Comparato, Giovanni Aragona, Maria Gabriella Marinone, Francesco Giangregorio, Michele Di Stasi, Fabio Fornari

Riccardo Solimando, Gian Maria Prati, Patrizia Perazzo, Giuseppe Comparato, Giovanni Aragona, Maria Gabriella Marinone, Francesco Giangregorio, Michele Di Stasi, Fabio Fornari, Department of Gastroenterology and Hepatology, Hospital "G. da Saliceto" Piacenza, Italy

Correspondence to: Fabio Fornari, Department of Gastroenterology and Hepatology, Hospital "G. da Saliceto", Piacenza, Italy.

Email: f.fornari@ausl.pc.it

Telephone: +39-0523-302058

Fax: +39-0523-302057

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This case illustrates the highly variable rate of HCC recurrence and progression after liver transplantation and raises interesting questions about its natural history and post-transplant surveillance.

Key words: Liver transplantation; Hepatocellular carcinoma; Metastasis; Hepatitis C virus; Sustained virologic response

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ABSTRACT

Recurrence rate of hepatocellular carcinoma is reported below 15%, mainly within 2 years after liver transplantation. We report an original case of a 62-year-old man with HCV-related liver cirrhosis, complicated by small uninodular hepatocellular carcinoma (HCC) completely eradicated by intraoperative thermal ablation in April 2003, who underwent liver transplantation in April 2004. The histopathologic analysis of explanted liver described an occult well differentiated uninodular HCC of 7 mm in diameter, without vascular invasion. Despite a sustained virologic response to antiviral therapy for recurrence of HCV infection in the graft and alpha-fetoprotein always within the normal range, in 2014 (10 years after liver transplantation) the patient developed brain and renal lesions, resulted as undifferentiated hepatocellular carcinoma recurrences at the histopathologic analysis. After a complete surgical resection of both recurrences, we introduced therapy with Sorafenib and exchanged immunosuppressive therapy from Tacrolimus to Everolimus, but six months later alpha-fetoprotein abruptly increased and total body computer tomography shown a significant progression of disease with recurrences in liver, spleen, lung and lymph nodes. Nevertheless, to date the patient is still alive.

INTRODUCTION

Liver transplantation (LT) is the first curative treatment for early stage hepatocellular carcinoma (HCC) in patients with cirrhosis because, unlike resection, may simultaneously cure the tumor and the underlying hepatic disease^[1]. According to Milan criteria in the selection of "optimal candidates" to LT, the recurrence rate of HCC is reported below 15%^[2]. Most recurrences appear within 2 years after LT; before transplant, the tumor factors associated with higher likelihood of recurrence are diameter > 5 cm, poor differentiation and vascular invasion^[3,4]. The majority of recurrences occur within the donor liver, even if an extra-hepatic site may be involved in 10-43% of patients^[4].

CASE REPORT

A 62-years-old man with a history of genotype 1b hepatitis C infection and liver cirrhosis Child-Pugh A5 developed a sub-capsular uninodular liver lesion of 16 mm in diameter at segment II in January 2003, which was defined by US-guided fine needle aspiration biopsy as a well differentiated HCC. Three months later he was submitted to

an intraoperative radiofrequency thermal ablation of the lesion.

In April 2004 he underwent orthotopic liver transplantation. As a result of intraoperative detection of non-neoplastic portal vein partial thrombosis, a life-long anticoagulation therapy was prescribed. The histopathologic analysis of explanted liver described a partially encapsulated well differentiated uninodular HCC of 7 mm in diameter at segment VIII, without vascular invasion or satellites. The immunosuppressive therapy with tacrolimus (0.5 mg bis in die) was prescribed.

Recurrence of HCV infection was demonstrated in October 2006 (high viral load: 5.124.580UI/mL). The patient was submitted to liver biopsy that showed high grade of fibrosis (F3-F4 according to Ishak score). In July 2007, the patient was started on a 48-week anti-viral treatment (Peg-IFN-alpha2a 180 µg/week plus Ribavirin 1000mg/die), obtaining a sustained virologic response (SVR). Subsequent clinical, laboratory, ultrasonographic and dynamic Computer Tomography (CT) surveillance were normal. In March 2013, the dynamic CT showed a 14 mm sized round and well-defined hypodense nodular lesion in the cortex of the right kidney without arterial enhancement, defined as a complex renal cyst, deserving close monitoring (Figure 1). Serum alpha-fetoprotein (AFP) levels were always below 10 ng/mL during follow up.

In September 2013 the patient was admitted to our department because of an intense, atraumatic, sudden knife-like pain on his right flank. Dynamic TC showed a 10.5 cm peri-renal hematoma departing from the upper pole of the renal cortex and supplied by a small venous blood vessel (Figure 2).

The laboratory tests revealed mild anemia (Hb 12.7 gr/dL) with a therapeutic INR value (2.29). Prompt INR correction with vitamin K arrested active bleeding, resulting in gradual hematoma reabsorption, as documented by the following CT controls, the latter of which was performed without the use of contrast medium. The patient was discharged with the diagnosis of spontaneous rupture of renal cyst under anticoagulation therapy that required discontinuation of warfarin.

Five months later (February 2014), the patient had an emergency admission for severe headache and right temporal hemianopsia. An urgent cerebral CT described a large edema of the left cerebral hemisphere, with an inhomogeneous hyperdense area of 35 mm inside, with contralateral shift of the cerebral midline (Figure 3). Suspecting brain metastases, as suggested by a subsequent Magnetic Resonance Imaging (MRI), a total-body TC was performed to highlight a possible primary tumor: unexpectedly, a 45-mm coarse solid malignancy was identified at the upper pole of the right kidney, adjacent to the previous hematoma (Figure 4).

No other lesions were identified. Serum AFP level was strongly increased for the first time (267.9 ng/mL) rising up the suspicion that lesions were both extrahepatic late recurrence of HCC. The histopathologic analysis of the cerebral mass lesion after the emergency intracranial tumorectomy (March 2014) confirmed the diagnosis of undifferentiated metastatic HCC. The patient's postoperative course was uneventful and he gradually regained the ability of movement and the right vision. After cerebral metastasis surgical resection, the patient's serum AFP level partially decreased to 104.3 ng/mL. No other lesions were identified on positron emission tomography (PET) and bone scintigraphy at that time, except for the already known renal mass.

In May 2014, the patient underwent right nephrectomy and histopathologic examination confirmed once again the presence of metastatic undifferentiated HCC (immunohistochemistry positive for antibodies anti-hepatocyte and anti-polyclonal carcinoembryonic antigen [pCEA]) (Figure 5).

After nephrectomy, the patient's AFP level decreased to 43 ng/mL. However, on the scheduled follow up examination six months later, the AFP level had quickly increased up to 1885.8 ng/mL, despite the introduction of kinase inhibitor drug Sorafenib and the exchange of immunosuppressive therapy from calcineurin-inhibitor Tacrolimus to mammalian target of rapamycin inhibitor Everolimus (Figure 6).

Total body CT performed in November 2014 confirmed the presence of focal lesions in each hepatic lobe, in spleen, in the left lung and multiple lymphadenopathies on the both sides of the diaphragm, all of them strongly suspicious for metastasis (Figure 7).

Nevertheless, to date the patient has a good quality of life – except for temporary hand-foot syndrome, that required to stopping Sorafenib – and continues outpatient visits at our department. The last US, performed in February 2016, documents further diffusion of neoplastic lesions, with left hepatic lobe and splenic parenchyma almost completely infiltrated, recurrences in the right hepatic lobe, mediastinum and abdominal lymph nodes. At this time, AFP level is 15.124 ng/mL.

DISCUSSION

Liver transplantation is the established curative therapeutic option for HCC, as it provides complete oncologic resection and correction of the underlying liver dysfunction^[1]. Since the adoption of Milan criteria in 1996, liver transplantation for HCC has been associated with an excellent long-term outcome, with a 5- and 10-year survival of 73% and 70%, respectively^[4]. Nevertheless, tumor recurrence occurs in 3.5% to 21% of recipients, despite careful pre-transplant staging and patient selection, and represents one of the major drawbacks for long-term survival, with a median survival period of 5 months by the onset of the recurrence^[5].

More than eighty percent of recurrences occur within the first 2 years of LT, with a median time of 8 to 14 months^[6]; they can involve not only the graft, but also extrahepatic organs such as lungs, bone, lymph nodes, adrenal glands and peritoneum, in descending order of frequency^[4]. Very late recurrences (i.e. ≥ 5 years after LT) are unusual and only a few cases are reported in the literature. The observational study of Roayaie et al highlighted that, among 59 patients with a recurrence, only 6 (10%) patients developed a recurrence 4 or more years after transplantation^[3]. In addition, only two previous case reports describe recurrences occurring over 10 years after LT^[7,8]. Beyond the Milan criteria, other HCC factors associated with late recurrence are small tumor size, absence of microvascular invasion and well to moderate HCC differentiation: all these features are present in our case^[4]. Furthermore, our patient obtained a SVR after treatment for HCV recurrence in the graft, turning off chronic hepatitis with advanced fibrosis before the development of cirrhosis, both conditions considered risk factors for intrahepatic HCC recurrence^[9]. In a recent large scale cohort study of 33,005 HCV-infected patients submitted to anti-viral treatment, in the individuals who achieved SVR a considerable reduction in HCC risk^[10] was observed, with an overall incidence rate of 0.33% per year versus 1.32 % in the group of patients with no SVR. In these patients the highest risk of developing HCC was associated with the presence of cirrhosis (HR = 6.69). On the other hand, the first site of recurrence of HCC in our patient was extrahepatic and therefore the role of hepatic disease was without relevance.

The natural history and prognosis of late HCC recurrences after LT are not well understood. Several studies have noted more favorable outcomes and an improved 3-year and 5-year survival compared to early recurrences (40% vs 8% and 71% vs 7% respectively)



Figure 1 Abdominal CT revealed hypodense nodular lesion in the cortex of the right kidney (white arrow). A: arterial phase; B: venous phase; C: delayed phase.

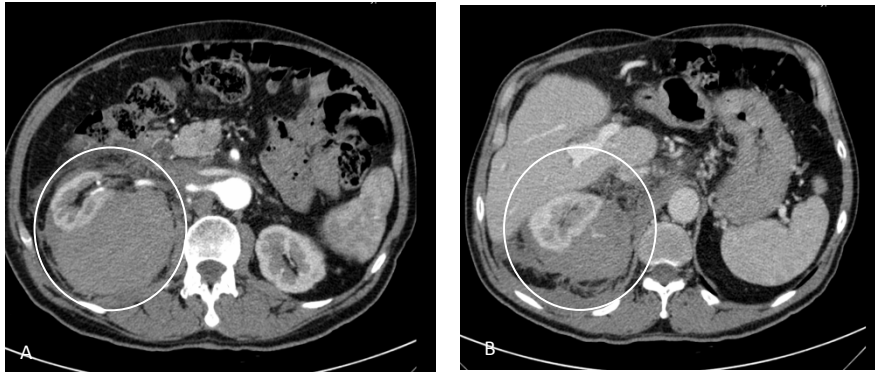


Figure 2 Abdominal CT revealed a 10 cm sized gross perirenal hematoma supplied by a venous vessel (white ring). A: arterial phase; B: venous phase.

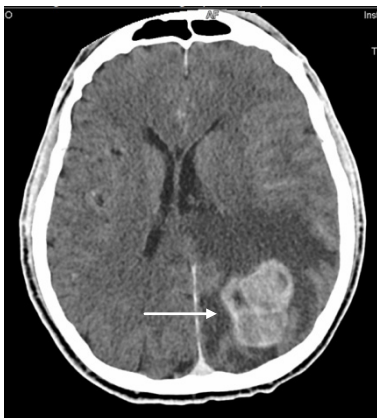


Figure 3 Cerebral CT revealed a 3.5 cm inhomogeneous solid lesion of the left hemisphere (white arrow).



Figure 4 Abdominal CT revealed a 4.5 cm coarse solid lesion at the upper pole of the right kidney, with adjacent residue of previous hematoma (black arrow).



Figure 5 Gross findings of the right kidney revealed a well-circumscribed yellowish ovoid mass within the Gerota's capsule, measuring 6.5 cm. The cut surface of the mass showed multiple necrotic foci in the diffuse homogeneous background.

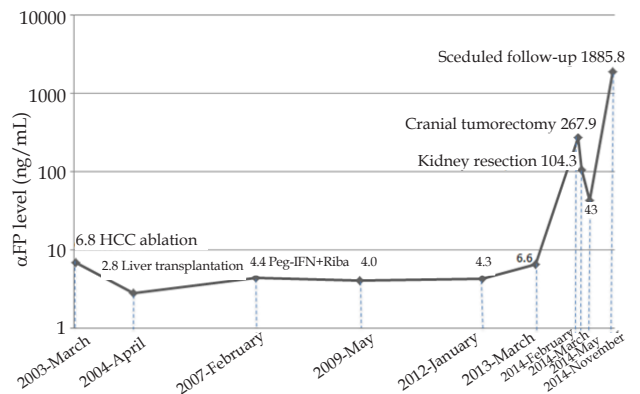


Figure 6 The patient's AFP level. The patient's AFP level was closely correlated to occurrence of extrahepatic metastases and surgery.

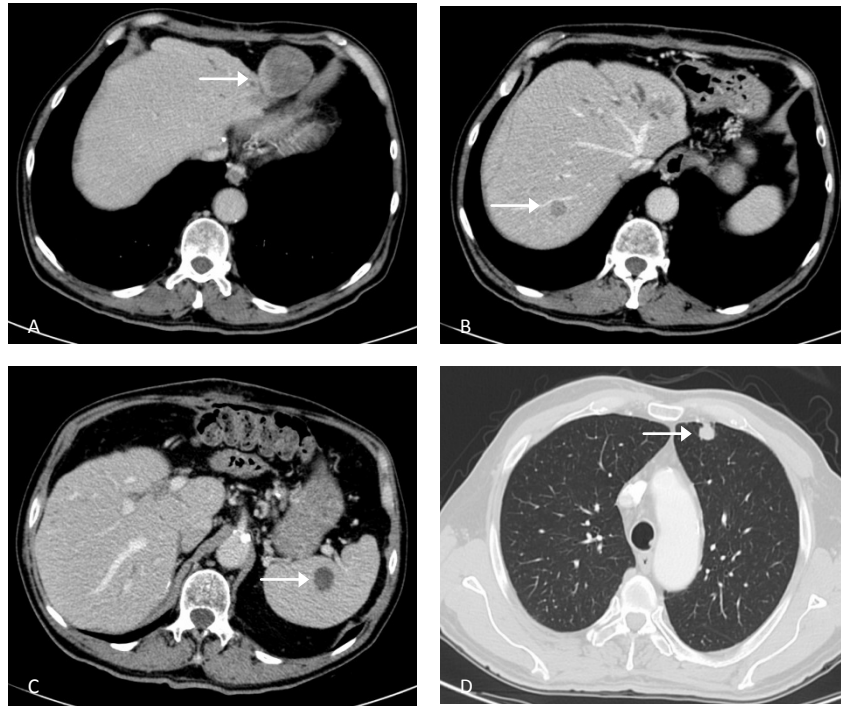


Figure 7 Late recurrences after liver transplantation. Left (A) and right (B) hepatic lobe recurrence; splenic (C) and left lung (D) metastasis.

^[11,12], which might indicate perhaps a more indolent tumor biology; on the other hand, other studies have described late recurrences as more biologically aggressive, with a decreased tumor doubling time, caused by histopathological changes (from moderate to poor differentiation degree) between the primary and the recurred HCC^[13]. Our case seems to confirm these latter findings. The histopathologic analysis of both HCC nodules submitted to intraoperative ablation in 2003 and found in the explanted liver in 2004 showed a high degree of differentiation, while the HCC recurrences in the brain and right kidney ten years later were poorly differentiated and biologically more aggressive. In fact, only six months after surgical resection of both recurrences, AFP promptly increased and the CT showed an abrupt disease progression, as confirmed by the last abdominal ultrasound.

This evidence seems to redefine the usefulness of post-LT surveillance and treatment of HCC recurrence. Several studies have shown that an aggressive screening protocol after LT allows early detection of localized and resectable HCC recurrence, which could be susceptible to a possibly curative surgical treatment^[14,15]. Indeed, multivariate analysis revealed that surgical treatment is independently associated with prolonged survival (HR 2.5, $p = 0.016$)^[4]. However these findings were observed in transplant recipients with early recurrence of HCC, which mainly shows intrahepatic localization, but not in patients with late recurrence with extrahepatic spread, less liable to a therapeutic intervention^[12]. Furthermore, surgical treatment of recurrences rarely results in complete eradication of HCC. Castroagudin *et al*^[6] described the outcome of recipients with late extrahepatic recurrences (> 5 years after LT) undergoing surgical treatment. Although recurrence was limited and surgically removed, disease-free survival was poor. This figure is consistent with the short time (6 months) between surgical resection of HCC recurrences and disease progression observed in our case. This evidence agrees with the fact that HCC recurrence could become poorly differentiated and tumor doubling time decreases with increasing tumor stage, with biological behavior similar to advanced HCC in non-transplanted

patients.

The phenotypic transformation observed in the metastatic lesions compared to the primary tumor and the late recurrence of HCC after transplantation could be probably correlated, although this correlation is not fully understood. It is hypothesized that during the early phases of HCC development, some HCC cells with undifferentiated phenotype metastasize the bone marrow via bloodstream and survive there for a long time in a dormant state, induced by the unfavorable microenvironment and the angiogenesis inhibition^[16]. Intrinsic factors, such as stiffness environment (eg. that encountered in the fibrotic allografts), and extrinsic factors, such as injury or surgery^[17], may be responsible for the reactivation of dormant tumor cells. The process of reactivation from dormancy, which may involve the mesenchymal-to-epithelial transition, after the epithelial-to-mesenchymal transition undergone by the malignant cells to enter the dormancy state could explain the histopathological changes between the primary and the recurred HCC and its aggressive behavior^[8].

CONFLICT OF INTEREST

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