Article type : Clinical Observations in Hepatology

Could autoimmune disease contribute to the abscopal effect in metastatic hepatocellular carcinoma?

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1002/HEP.31186](#)

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Introduction

The abscopal effect is defined as regression of untreated metastases after a local treatment such as surgery or radiotherapy. Although this effect has been described in various tumors, it is very rare in hepatocellular carcinoma (HCC) with only a few reported cases in the literature. Moreover, little is known about the contribution of the immune state of the host in relation to this phenomenon. We report this case of sustained complete remission of metastatic HCC after irradiation of a bone metastasis in a patient with autoimmune liver and lung disease.

Presentation of the Case

In June 2016, a 58-year-old woman consulted because of progressive cervical pain of several weeks' duration. CT and MRI of the cervical spine revealed a malignant osteolytic lesion at C2 without signs of spinal cord compression. Further staging with ^{18}F -fluorodeoxyglucose (^{18}F -FDG) PET/CT revealed a large liver lesion in segment 7 and an additional bone metastasis in the left femur (figure 1A). Blood tests showed elevated liver enzymes (gamma glutamyltransferase 445 IU/L; alanine aminotransferase 51 U/L) with bilirubin within normal range. Serologic screening for underlying liver diseases showed no past or active hepatitis B or C infection. ANF titer was elevated ($>1:1280$) as were anti-smooth muscle antibodies ($>1:80$). Anti-liver-kidney-microsome antibodies and anti-mitochondrial antibodies were negative. Alpha-fetoprotein (aFP) was markedly elevated (1717 $\mu\text{g/l}$). Biopsy of the liver lesion revealed the presence of a poorly differentiated HCC. Final diagnosis was advanced HCC with underlying type 1 autoimmune hepatitis.

The patient underwent palliative radiotherapy (32 Gy; 8 x 4 Gy) from C1 to C4. Five days after the last session, aFP levels dropped to 28 $\mu\text{g/l}$. MRI of the liver showed a decrease in liver lesion size with marked central necrosis and only limited contrast uptake. ^{18}F -FDG PET/CT 3 months after radiotherapy confirmed a complete metabolic response in all known lesions (figure 1B). aFP levels were within normal range. Two years later, recurrent malignancy was suspected on a follow-up PET/CT with several new hypermetabolic lung lesions (figure 2). However, biopsy only showed pronounced inflammation with a polytypic lymphoplasmocytic infiltrate. More than 3 years after initial presentation, there is no evidence of HCC recurrence. Patient is asymptomatic with regard to her autoimmune disease and no immunosuppressive drugs have been initiated.

Discussion

We present a case of spontaneous complete remission of metastatic HCC after palliative irradiation of a bone metastasis. The mechanism behind this rare event is thought to be immune mediated (1). Radiation induced DNA damage leads to cell death by apoptosis thereby releasing tumor cell-derived antigens. Cytotoxic T-cells recognize these antigens, become activated and circulate through the bloodstream to attack remaining distant tumor cells that express the same tumor antigens. T-cell activation is further stimulated by irradiated tumor cells through interferon signaling (2).

The phenomenon seen in this patient is rare because effective T-cell priming is hampered by the immunosuppressive tumor microenvironment. The liver specifically is considered tolerant for neo-antigens and chronic inflammation due to liver diseases additionally causes immune exhaustion (3). Immunologically “hot” tumors such as malignant melanoma have been associated more frequently with spontaneous regression. Vitiligo, an autoimmune disease of the skin, is associated with a reduced risk of melanoma and other cancers (4). So the question arises whether an autoimmune constitution in this case has contributed to an antitumor immune response. Earlier case reports of spontaneous regression of metastatic pancreatic adenocarcinoma and renal cell carcinoma in patients with lupus and psoriatic arthritis suggested a similar association (5). With this in mind, it seems cautious not to treat this patient with immunosuppressive drugs despite the clear risk associated with progression of autoimmune hepatitis. In general, little is known about the contribution of host characteristics to antitumor immune response, including in patients treated with immunotherapies.

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Figure legends

Figure 1: (A) ^{18}F -fluorodeoxyglucose PET and CT images before palliative radiotherapy of the cervical bone metastasis shows a large hypermetabolic liver lesion in segment 7 (SUV_{max} : 10.1) and an additional bone metastasis in the left femur (SUV_{max} : 7.0). MRI of cervical spine demonstrate a large expansive metastatic bone lesion in C2 (dens and body of C2) on the un-enhanced T1 weighted sequence in the transverse plane with a low signal intensity of the lesion. (B) FDG PET/CT 3 months after radiotherapy shows complete remission of all lesions. MRI showed decrease of the volume of the bone metastasis in the dens and in the body of C2.

Figure 2: Development of multiple lung lesions 2 years after radiotherapy. Biopsy revealed an inflammatory infiltrate.

Figure 1

Figure 2