''Hockey Stick'' may Strike Back: Hepatocellular Carcinoma on Noncirrhotic Liver as a Late Toxicity of Lombo-Aortic Radiotherapy for Seminoma. A Review Triggered by an Unusual Case

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Most patients with testicular seminoma have been treated with a curative intent for decades. Second cancers after radiotherapy for testicular seminoma before 1990 are a growing issue, and are related to previous generation of dose planning and delineating strategies. Among those cancers, hepatocellular carcinoma is an extremely rare occurrence, especially when affecting patients with healthy, noncirrhotic liver. Here, we describe such a case in a patient of our institution, and subsequently review the relevant literature and large epidemiologic studies. Understanding those late and serious toxicity features may help cancer care teams to screen and treat those patients appropriately. (J Clin Exp Hepatol 2016;6:54–58)

Major improvement in testicular cancer treatment in the second half of the 20th century made it a curable disease, mainly thanks to platinum-based chemotherapy and radiation therapy.[1,2] Cancer of the testis has one of the best 5-year survival rate.[3,4] Avoiding long-term iatrogenic morbidity is now part of the treatment plan. Among the many malignancies arising from the radiotherapy field of previously treated testicular cancer patients, hepatocellular carcinoma is a rare occurrence. We describe a case of a patient presenting with in-field hepatocellular carcinoma 34 years after radiotherapy for testicular seminoma.

CASE REPORT

A 62-year-old man presented in April 2013 with dehydration and acute renal failure. Relevant medical history reported a left testicular seminoma in 1979, for which he underwent left orchidectomy, adjuvant platinum-based chemotherapy, and radiotherapy. Other history included transient ischemic attack in 2002. He had lost 8 kg over the past 8 months. On examination, there was no symptom of portal hypertension or chronic liver failure. Abdominal ultrasound (US) found a heterogeneous liver mass. Thoracic and abdominal computerized tomography scan (CT scan) found a 16 cm great axis tumor occupying left liver lobe almost entirely, associated with left portal thrombosis (Figure 1). The thrombus was believed to be of tumorous nature. Angio-CT scan of the liver confirmed the invasion of the left portal vein branch by the tumor. The Right liver lobe was not affected and presented normal radiological features. No distant metastases were found. Gastroscopy and colonoscopy showed no suspicious lesions. Alpha-fetoprotein level was 374,000 ng/mL. Other tumor markers were within normal range. Liver biopsies were performed. Pathology report came to the conclusion of a well-differentiated hepatocarcinoma (Figure 2). Liver function test were unaffected. Every major cause of cirrhosis and liver disease was ruled out including alcoholic cirrhosis, autoimmune hepatitis, hemochromatosis, Non-Alcoholic Steato-Hepatitis (NASH) or fatty liver disease, primary biliary cirrhosis, sclerosing cholangitis, and Wilson's disease. Viral serologies were negative for hepatitis B (HBs antigen and HBc antibody), hepatitis C, and cytomegalovirus (CMV), and there were no clinical suspicions of viral hepatitis. No aflatoxin exposure was found. 15 min Indocyanin green (IG) dye retention rate was 9.3% (normal range below 10%) and IG clearance was slightly low at 14.6% (normal range between 18 and 20%). The liver was thus considered healthy and noncirrhotic. Preoperative liver MRI described heterogeneous, T1 hyposignal, and T2 hypersignal lesions occupying the left liver lobe in whole, but confined into it. Coronal enhancement and delayed contrast washout were featured. Of note, right lobe parenchyma appeared homogeneous without any signal anomaly even on early arterial acquisition. After

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Abbreviations: CT: computed tomography; NASH: nonalcoholic steatohepatitis; SEER: Surveillance, Epidemiology and End Results; TGCT: testicular germ cell tumor; US: ultrasound
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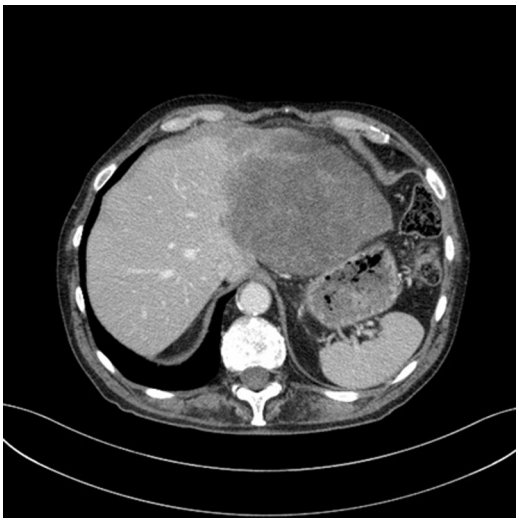

Figure 1 Left hepatic tumor within the radiotherapy field.

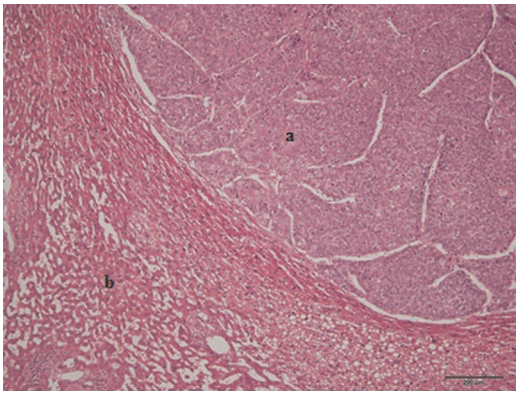

Figure 2 Hepatocarcinoma (a) next to healthy liver parenchyma (b).

multidisciplinary meeting, the patient was considered fit for surgery. Patient treatment plan consisted in complete surgical resection along with omentectomy and haemostatic splenectomy in June 2013 in a high-volume hepatic surgery center. Pathology report diagnosed a moderately differentiated, stage IV, pT4N0M1 hepatocellular carcinoma with omental metastases and vascular involvement, strongly stained positive for α-fetoprotein[5] (Figure 3), with a histological grade Edmonson and Steiner II. Myc gene amplification[6] was not present. Biopsies on adjacent liver showed no signs of hepatic disease (including neither cirrhosis nor hepatocellular carcinoma). There was no histological evidence of hepatic venous outflow tract obstruction, such as periportal or perivenular fibrosis, areas of infarction, and compensatory regenerative nodular hyperplasia. Surgical removal was considered adequate and close follow-up was set up. July 2013 CT scan showed metastatic recurrence in lung and patient was treated with sorafenib, until tumor progression in October 2013. Treatment then consisted in chemotherapy (oxaliplatin, gemcitabin) with an initial partial response followed by a disease progression (liver and lung) after 6 months. Because of ECOG, performance status was still rated 1; a third treatment line with pegylated liposomal doxorubicin along with 5-FU was conducted during 3 months before disease progression. Patient died in October 2014, 18 months after the initial diagnosis. The median survival for stage IV hepatocellular carcinoma is 10.7 months.[7]

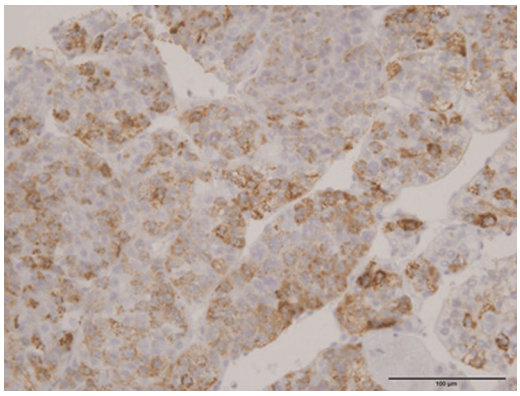

Figure 3 Alpha-fetoprotein stain.

Reviewing patient file, we took a closer look at the initial oncological workup that was carried through in 1979–1980 in order to treat his left testicular seminoma. At that time, patient underwent left orchidectomy, followed by platinum-based chemotherapy and photon-based external beam radiation therapy from January to February 1980. ''Hockey stick'', external beam photon radiation therapy of left iliac, and bilateral lombo-aortic lymph nodes were achieved (Figure 4). The dose was 40 Gy with a second radiation field on left renal hilum lymphadenopathy with a 45 Gy dose. In addition, 45 Gy irradiation of bilateral supraclavicular fossa was performed. Many nontarget organs were within the field limits: bladder, small bowel, pancreas, stomach, and left liver. Radiation induced cystitis and proctitis occurred as late toxicity.

In our diagnostic workup, we noted that the HCC had developed within an area that had been previously irradiated. Our patient had no precancerous lesion of the liver. Knowing that hepatocellular carcinoma occurring on a healthy liver is a rare disease, we hypothesized an association with the external beam radiation therapy on lombo-aortic lymph nodes performed some 30 years before.

REVIEW AND DISCUSSION

We looked for other cases of second primary liver cancer occurring after radiation therapy for testicular cancer and found no similar case. The closest paper we found was a series of 3 German patients who developed biliary tract malignancy between 18 and 32 years after being treated with radiotherapy for seminoma or bladder cancer.[8]