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Synchronous Primary Tumors of the Liver and Gallbladder: Case Report and Review of the Literature

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Abstract

As the longevity of human's increase and with scientific medical advances the occurrence of multiple primary malignant tumors (MPMT's) will rise. Synchronous multiple primary malignant tumors are defined as the occurrence of two primary neoplasms within six months of each other. Overall, the occurrence of MPMT's varies from 1%-16%, with HCC and multiple other tumors very rare and the synchronous occurrence of HCC and gallbladder carcinoma has only been reported 6 times. It is crucial to patient care that each tumor is identified correctly as they are treated entirely different and the prognosis for the patient is dependent on the stage for each.

Introduction

The occurrence of multiple synchronous primary tumors in patients with HCC is extremely rare and the association HCC and GBC has only been previously reported 6 times.

Criteria for the classification of multiple primary tumors: 1) each tumor is unequivocally malignant 2) each tumor is a separate and distinct entity 3) must exclude that one is a metastasis from the other [1]. It is critical that simultaneous tumors be identified as therapy must be guided taking into consideration both tumors and the treatment for each independently, as well as the treatment for both combined. A thorough review of the literature in PubMed was performed and articles relevant to this case report cited.

Case Presentation

An elderly male was referred to our institution after computerized tomography (CT) scan revealed a suspicious mass in the dome of the gallbladder and he was scheduled for a laparoscopic versus open cholecystectomy with possible radical cholecystectomy. No hepatic lesions were noted on CT. At the time of the laparoscopic surgery the surgeons were unable to completely visualize the gallbladder secondary to dense adhesions therefore an open cholecystectomy was performed. After careful dissection, the gallbladder was isolated and a firm mass was palpated in the fundus. The node of Calot was dissected and sent to pathology for an intraoperative frozen section which was positive for carcinoma. A radical cholecystectomy was performed which included additional lymph node dissection and resection of segment 4 of the liver. The procedure and postoperative care of the patient was excellent and there were no complications. The patients care was transferred to a different facility but he was stable one year later with no definitive recurrence of the two tumors.

The gross specimens consisted of a partial hepatectomy 5 cm x 4.5 cm x 4 cm with a poorly circumscribed 2.5 cm tan yellow mass in the background of a cirrhotic liver. The gallbladder consisted of a 10 cm x 6 cm x 4 cm gallbladder with a mass consisting of multiple fragments of friable red papillary tissue in aggregate 4 cm x 3 cm x 2.5 cm. Microscopically the HCC consisted of thickened trabeculae (some 8-10 cells thick) comprised of moderately atypical hepatocytes with prominent nucleoli, nuclear pseudoinclusions and mitoses (Figure 1). The gallbladder consisted of a moderately differentiated adenocarcinoma that predominantly formed glands although there are nests of cells infiltrating the gallbladder wall (Figure 2). The GBC was positive for CEA (Figure 3), CK7, CK20 while the HCC was negative for these markers. The HCC was intensly positive for AFP.

Discussion

As the longevity of human's increases and medical science capabilities improve the occurrence of multiple primary malignant tumors (MPMT's) will also increase. There are three established criteria

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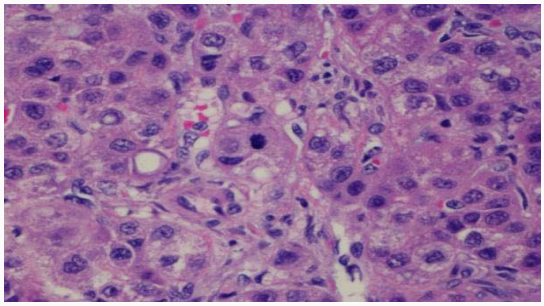

Figure 1: Hepatocellular carcinoma with thickened trabecula, pleomorphic hepatocytes, mitosis in the center.

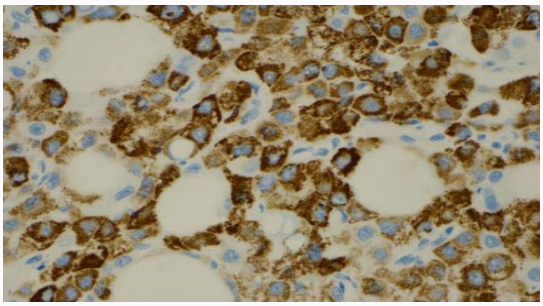

Figure 2: Hepatocellular carcinoma positive for alpha-fetoprotien.

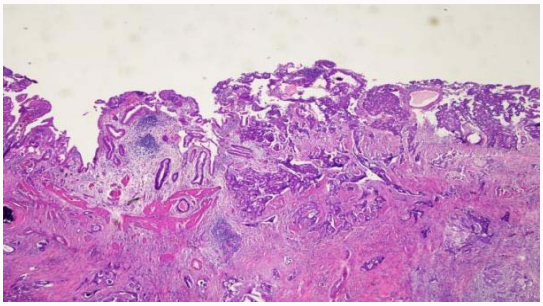

Figure 3: Gallbladder with adenocarcinoma.

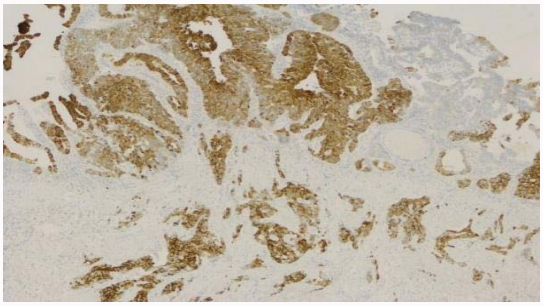

Figure 4: Gallbladder positive for CK7 (CK20 and CDX2 stained positive also).

Table 1: IHC demonstrated that the two tumors are phenotypically distinct and thus one is not a metastasis from the other.

Immunohistochemistry	CK7	CK20	CDX2	AFP
Gallbladder carcinoma	+	+	+	-
Hepatocellular carcinoma	-	-	-	+

for the classification of multiple primary tumors: (1) each tumor is unequivocally malignant (2) each tumor is a separate and distinct entity (3) must exclude that one is a metastasis from the other. These criteria were first put forth by Warren and Gates in 1932 and for the most part still remain valid [1]. With today's modern immunohistochemistry and genetic analysis the latter two criteria are easily met and mutually exclusive. Synchronous tumors are defined as tumors that occur within 6 months of each other and metachronous tumors occur greater than 6 months of each other. In the present case the hepatocellular carcinoma (HCC) and the gallbladder carcinoma (GBC) occurred simultaneously, there was no clinical or histological connection between the two and IHC demonstrated that the two tumors are phenotypically distinct and thus one is not a metastasis from the other (Table 1).

The occurrence of MPMT's varies considerably, between 0.734% and 11.7% as documented by Demandante et al. [2] in a literature review of 1,104,269 patients with MPMT's and the incidence of synchronous MPMT's is rare. Bagri reported that out of 23,260 patients, 41 had MPMT's and only 9 were synchronous (< 0.04%) [3]. Papaconstantinou et al. [4] reported on a twelve year period and the incidence was 0.5%, 39 out of 7516. An in-depth and thorough SEER report stated the incidence varied depending on the site of the initial primary and was 1% for liver to 16% for bladder [5].

The occurrence of additional multiple primary tumors in patients with HCC are extremely rare and the association HCC and GBC has only been previously reported 6 times. De Pangher Manzini et al. [6] reported that over a fifteen year period from 1980-1995 there were 29 cases of HCC and MPMT's, and in two of these cases the additional tumor was GBC. Wei et al. [7] reported on a series of patients who had HCC and the associated MPMT's. Over a 26 year period 448 HCC's were identified, 40 had MPMT's, only 11 had synchronous tumors (about 2.5%) and there was a single case of HCC and GBC (0.22%). Imada et al. [8] reported on a case of triple carcinomas; HCC, GBC and cholangiocarcinoma. Kim et al. [9] reported on a case in which a patient underwent a partial hepatectomy and at the time of surgery an intraoperative frozen section discovered an adenocarcinoma of the gallbladder and La Greca et al. [10] discovered a GBC after resection for HCC.

Although simultaneous HCC and GBC is extremely rare it is imperative that they both are identified as the treatment and prognosisis radically different for each one. The basic concepts involved in treating a patient with both HCC/GBC can be applied to any patient with MPMT's, ie whether surgery, chemotherapy, immunotherapy or radiation is the desired treatment. For example, transplant or partial hepatectomy are the primary treatment options for HCC with the greatest chance of success. However, less than 30% of GBC is amenable to surgical resection [11] which greatly limits surgery as a treatment option in HCC. Cytotoxic chemotherapy such as gemcitabine is used in GBC but chemotherapy is generally not beneficial in HCC [12,13]. Sorafenib, an inhibitor of the mitogen-activated pathway, is the only approved chemotherapy agent in HCC however it is potent bone marrow suppressor and even if it was not harmful in GBC, the addition of cytotoxic chemotherapy with the immunologic would be especially harmful to the bone marrow.

Although extremely rare concurrent HCC and GBC are treated entirely different and their occurrence's should be recognized pathologically and clinically. This case superbly demonstrates the multifaceted aspects of treating patients with multiple primary tumors and as the longevity of human's increase, and with the capabilities of the medical profession rapidly advancing, multiple primary

malignant tumors will probably become more commonplace.

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