

# Hepatoid Adenocarcinoma in Gallbladder: A Case Report

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## ABSTRACT

Hepatoid adenocarcinoma is a rare extrahepatic tumor, resembling hepatocellular carcinoma. It resembles hepatocytes both morphologically and functionally. Serum level of AFP is high in most cases. They reveal positive immunostaining with AFP, CEA, CK-8 and CK-18. To make the diagnosis of Hepatoid adenocarcinoma, hepatocellular carcinoma should be ruled out. Although it has an aggressive natural history, some cases like ours may show slower course, and recur in distant sites. In this article, we present a case of ovarian Hepatoid adenocarcinoma who presented with tumor in gallbladder having similar histopathology after 3 years of initial diagnosis.

Keywords: gallbladder, hepatoid adenocarcinoma, ovary, metastasis

## SAFRA KESESİNDE HEPATOİD ADENOKARSİNOM: OLGU SUNUMU

### ÖZET

Hepatoid adenokarsinom, hepatoselüler karsinoma benzeyen ve nadir görülen ekstrahepatik bir tümördür. Tümör hücreleri hem fonksiyonel hemde morfolojik olarak hepatositlere benzer. Çoğu olguda AFP serum düzeyi yüksektir. Tümör hücreleri AFP, CEA, CK-8 ve CK-18 ile pozitif immünboyanma gösterirler. Hepatoid adenokarsinom tanısı için hepatoselüler karsinom ekarte edilmelidir. Agresif bir doğal seyri olmasına rağmen bazen yavaş seyirli olabilir ve uzak yerlere metastazla hastalık tekrarlayabilir. Bu yazımızda over Hepatoid adenokarsinomu nedeni ile opere edilen ve 3 yıl sonra safra kesesinde Hepatoid adenokarsinom nüksü olan olguyu sunuyoruz.

Anahtar sözcükler: safra kesesi, hepatoid adenokarsinom, over, metastaz

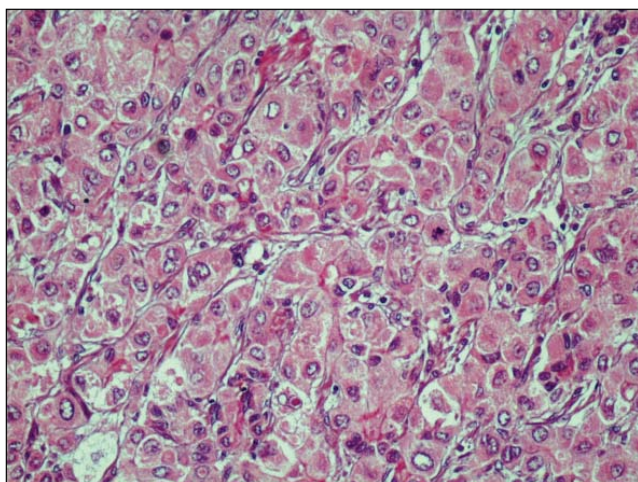
## Introduction

Hepatoid adenocarcinoma (HAC) is a rare extrahepatic tumor, resembling hepatocellular carcinoma. Cases differ in site of primary and in immunophenotyping. First case in literature was reported in gastric location in 1985 (1). Thereafter, ovarian, pancreatic, gall bladder and peritoneal cavity localizations have been described (2-5). Herein, we present a case of ovarian HAC who presented with tumor in gallbladder having similar histopathology after 3 years of initial diagnosis.

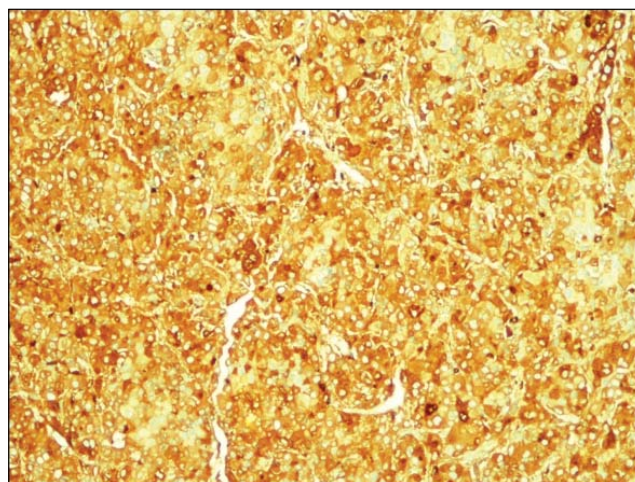
## Case Report

A 55 years old female patient had underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy

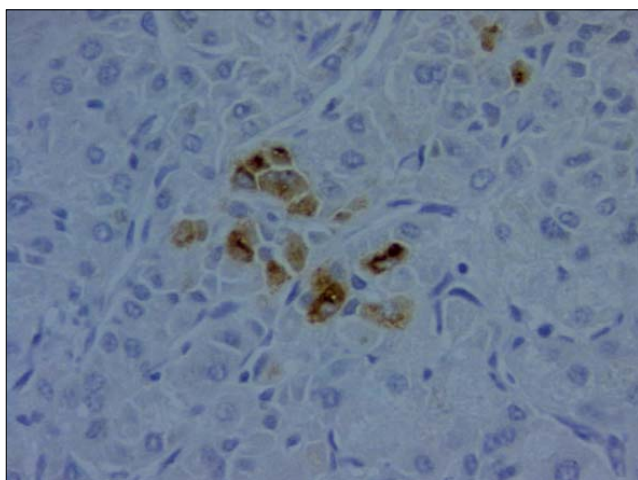
because of right ovarian mass 3 years ago. She was diagnosed histopathologically as ovarian HAC showing positive immunohistochemical (IHC) staining with  $\alpha$ -fetoprotein (AFP), cytokeratin-8 (CK-8), hepatocyte specific antigen (Hep-Par),  $\alpha$ -1 anti-chymotrypsin, and negative staining with inhibin, vimentin, CA-125 and carcinoembryonic antigen (CEA). She had been staged as FIGO stage IA disease and been given no further treatment. After 2 years of follow up with no remarkable problem, she got out of surveillance. Later, she presented again with right upper quadrant pain of 1 year of duration. There was no abnormal finding on physical examination other than incision scar in suprapubic area. Upper abdominal ultrasound (US) and magnetic resonance imaging (MRI) revealed a mass in the localization of gallbladder. Her laboratory tests revealed WBC of  $13.090 \times 10^3/\text{mm}^3$ , RBC of  $4.51 \times 10^6/\text{mm}^3$ , Hgb



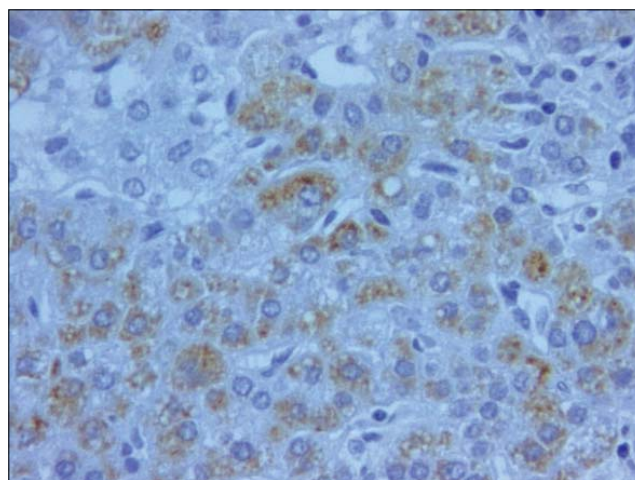
**Figure 1.** (10x20 HE Gallbladder). Gallbladder tumor shows trabecular arrangements of tumor cells with abundant eosinophilic cytoplasm, distinct cell borders, and nuclei with prominent nucleoli. Mitoses are easily identified.



**Figure 2.** (10x10 AFP Gallbladder). AFP immunohistochemistry shows diffuse and strong positivity.



**Figure 3.** (40x10 AFP Ovary) Focal but strong AFP positivity in ovarian tumor.



**Figure 4.** (40X10 Hep-Par1 Ovary) Ovarian tumor shows positive reaction with Hep-Par1.

of 12.8 g/dL, Hct of 39.3 %, MCV of 75.4  $\mu\text{m}^3$ , PLT of 336  $10^3/\text{mm}^3$ , BUN value of 12 mg/dL, serum creatinine of 0.7 mg/dL, lactate dehydrogenase of 217 U/L and AFP of >3000 ng/ml. Serological evaluation for HBV and HCV infections were non-reactive. She underwent cholecystectomy plus hepatic wedge resection and lymph node sampling. At the time of operation no other focus of tumor was detected. Histopathological evaluation of surgical specimen showed diffuse involvement of whole gallbladder except neck and surgical margin. There was no serosal invasion. Microscopic examination revealed poorly differentiated carcinoma of trabecular and sinusoidal architecture. Tumor cells showed appearance of hepatoid cells with mitotic figures, hyperchromatic round elliptical nucleoli and abundant eosinophilic cytoplasm. Immunohistochemical

studies were positive for AFP, HEP-PAR and CK-8 (Figure 1-4). The specimens from hepatic resection and lymph node sampling were all negative for tumor infiltration. Positron emission tomography/computerized tomography (PET/CT) scan revealed no abnormal FDG uptake other than operation site. Her postoperative AFP value was 10 ng/ml.

## Discussion

HAC is first described in stomach and stomach is the most common site for HAC. Other sites of origin are ovary, lung, gall bladder and pancreas in order of frequency. Most cases show high serum levels of AFP and positive immunostaining with AFP although few reports noted no AFP production. AFP production was observed both in serum and

IHC studies in our case, serum level declined in the tests done postoperatively.

AFP, an oncofetal protein, is elevated in both malignant [eg, hepatocellular cancer (HCC) and benign (eg, cirrhosis) hepatic diseases. High levels of AFP are also detected in diseases like yolk sac tumor, embryonal carcinoma, mediastinal germ cell tumors, where extra hepatic secretion of AFP may be seen. More rarely, AFP production may be observed in tumors of lung, pancreas, ovary, and stomach. Like morphological features resembling HCC, it shows functional similarities with HCC, and produces AFP and CEA.

Another tumor marker for cases with HAC is CEA. It has been reported to be high in 50-100 % of cases. IHC and blood chemistry tests were positive for CEA production in our case, too. Immunostaining with CK-8 and CK-18 is also positive for cases with HAC (6).

Epithelial ovarian tumors more commonly metastasize to paraaortic, external iliac and retroperitoneal lymph nodes through lymphatic spreading. Through hematogenous route, although rare, they may spread to liver, spleen and lung, and to a lesser extent, bone and central nervous system may be the site of distant metastasis. Metastasis to gallbladder is comparatively rare. At the time of first presentation, the patient was accepted as primary ovarian HAC because of no remarkable mass in liver, no sign of primary HCC, and findings confined to ovarian primary. The specimen obtained from the second operation was compared with the initial specimens and all morphological and IHC features showed some similarities. Primary HAC in gallbladder is reported to be 4% of all cases with HAC (7). There was no finding of distant metastasis in PET/

CT scan, and she was evaluated as Stage II according to the 7<sup>th</sup> version of AJCC staging system for gallbladder tumors. No adjuvant treatment is decided to be given and, the patient is being followed up asymptotically.

Cases of HAC are managed in the same manner with other adenocarcinomas. Lymph nodes, liver and lung are the most frequent sites of metastasis. Metastasis to gall bladder is extremely rare. Combination chemotherapy with paclitaxel and carboplatin has been used in some cases with ovarian HAC. Median survival ranges from 12 to 20 months (8). Initial presentation of our patient was FIGO stage IA ovarian HAC, and we decided to give no further treatment.

In conclusion, HAC is heterogeneous group of disease. It resembles hepatocytes both morphologically and functionally. Serum level of AFP is high in most cases. They reveal positive immunostaining with AFP, CEA, CK-8 and CK-18. To make the diagnosis of HAC, hepatocellular carcinoma should be ruled out. Although it has an aggressive natural history, some cases like ours may show slower course, and recur in distant sites.

### Acknowledgements

This study were presented partially at the "7<sup>th</sup> National Congress Of Medical Oncology, 2010, Antalya, Turkey" in Turkish language.

### Conflict of Interest

We have no personal or financial conflict of interest and have not entered into any agreement that could interfere with our access to the data on the research, or upon our ability to analyze the data independently, to prepare manuscripts, and to publish them.

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