Hepatoid Adenocarcinoma of the Retroperitoneal Cavity: a Case Report

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ABSTRACT

Hepatoid adenocarcinoma (HAC) is a rare type of extrahepatic adenocarcinoma with clinicopathological features resembling hepatocellular carcinoma (HCC). The most common site of HAC is the stomach, although it has also been reported in various organs, such as gastrointestinal tract, ovary, pancreas, lung, kidney, uterus, and urinary bladder. The minimum histological criteria of HAC are the abundant eosinophilic cytoplasm and the evidence of alpha-fetoprotein (AFP) production, although the results are not always positive.HAC has an extremely poor prognosis with only a few cases reported. We report a case of a 56-year-old woman who came to Cipto Mangunkusumo Hospital with chief complaints of lower abdominal pain and enlargement. The abdominopelvic ultrasonography (USG) and computed tomography (CT) scan showed tumor mass in lower abdominal and pelvic area without any significant abnormalities in other abdominal organs. Microscopically, the tumor was first diagnosed as poorly differentiated carcinoma, but after reevaluation and immuno-histochemistry (IHC) staining results suggested HAC of the retroperitoneal cavity.

Key words: hepatoid adenocarcinoma, retroperitoneal cavity, immunohistochemistry.

INTRODUCTION

Hepatoid carcinoma/hepatoid adenocarcinoma (HAC) is a unique type of carcinoma that arises outside the liver in the absence of a primary hepatic neoplasm, but resembles hepato-cellular carcinoma (HCC) both histologically, functionally, and immunohistochemically. HAC is a rare entity. Incidence of HAC is 0.38-0.73%.[1-3] Here in our center at Department of Anatomical Pathology Cipto Mangunkusumo Hospital, there are only two cases of HAC during five years (2009-2013).

The tumor was first described by Ishikura et al. in 1985 as a specific type of gastric cancer. Since then, HAC has been reported in various anatomic locations. Most HAC originated from the stomach (83.9%). The other origins of the tumor are rare, including gallbladder (3.7%), uterus (3.2%), lung (2.3%), urinary bladder (1.8%), esophagus and peritoneum (0.9%). HAC of the rectum, colon, testis, ovary, jejunum or ureter are <0.5%. The mean age of HAC patients is 63 years, with 2:1 male-to-female ratio.[2-5] We report a HAC of the retroperitoneal cavity in a 56-year-old woman.

The two basic diagnostic criteria are the abundant eosinophilic cytoplasm of the tumor cells that resemble HCC and the production of alpha-fetoprotein (AFP), although the results are not always positive. The diagnosis based on clinical and histologiccharacteristics can be difficult. A careful search for a primary malignancy is necessary. The clinical presentations of HAC

may vary greatly depending on the anatomic locations of the tumor. Usually it presents with signs and symptoms of an adnexal mass, such as progressive abdominal distension and lower abdominal pain.[3,4,6]

Microscopically, these tumors are characterized by solid sheets of large cells with abundant eosinophilic cytoplasm, centrally pleomorphic nuclei and distinct cellular borders. Mitoses, some even atypical, are frequent. In addition to its morphologic similarity to liver cells, hepatic differentiations of the tumor cells could be confirmed by several immunohistochemical markers. The tumor cells are positive for AFP and cytokeratin (CK) staining.[7-9]

We report a case of HAC of the retroperitoneal cavity in a 56-year-old woman which at first diagnosed as poorly differentiated carcinoma. In this rare tumor, we would like to highlight about the pathogenesis, histopathology and IHC staining requirements to diagnose this tumor. The aim to report this case is to share our experience and an update about this entity.

CASE REPORT

Mrs. M, a 56-year-old woman came to Pasar Rebo Hospital on March 2012 with a chief complaint of abdominal discomfort since one month before admission. She had no history of other cancer, but her first daughter died because of breast cancer.

Patient underwent abdominopelvic USG and the result revealed pelvic mass, suspected uterine myoma. The doctor performed laparatomy surgery and found a tumor mass above the uterus, which attached to the mesentery and penetrated until recto-uterine space (Pouch of Douglas). Both of the ovaries and fallopian tubes were normal. Patient didn't receive any chemotherapy after the operation.

The results of anatomical pathology assessment in Pasar Rebo Hospital: gross examination presenting fragmented tissues with the size between 1,5x2x2,5 cm-2,5x5x6 cm, firm in consistency, and yellowish-white color. Histopathology examination revealed epithelial malignant tumor mass arranged in small nests and cords structure. Tumor cells had abundant eosinophilic cytoplasm and distinct cell borders. The nuclei was pleomorphic and vesicular, with prominent nucleoli. Mitosis was found. Fat and fibrovascular tissues were also infiltrated by tumor cells. The conclusion was high grade carcinoma, suspected from kidney.

Patient came to CiptoMangunkusumo Hospital on October 2012 with chief complaints of abdominal discomfort and abdominal enlargement since three months before admission. Clinical examination found a mass in lower abdomen. Patient underwent blood laboratory tests and the results of serum tumor marker were within normal range (table 1). Pelvic USG examination showed a solid mass in the pelvic cavity, the size was 12,3x13,8x11,6 cm, suspected to be a non-gynecological tumor (Figure 1). Abdominopelvic CT scan result showed a malignant mass, suspected carcinoma of the ovary or malignant lymphoma (figure 2). No abnormalities were seen on the bladder, uterus, liver, kidneys, and intestines.

Table 1. Patient's blood laboratory test results.

Laboratory test	Result	Normal value range
CEA (colon)	3,60	0-4,6 ng/mL
Ca 19-9 (pancreas and biliary)	17,4	<27 U/mL
Ca 125 (ovary)	4,57	0-35 U/mL
AFP (liver)	1,3	<5,8 IU/mL
HbsAg	Non-reactive	-

Based on standard operating procedure, the microscopic slide specimens from Pasar Rebo Hospital were reevaluated by Cipto Mangunkusumo Hospital pathologist. Histopathology examination revealed highly cellular malignant tumor mass with solid structure. Tumor cells had large, pleomorphic, and hyperchromatic nuclei, with prominent nucleoli. Mitosis easily found. Tumor cells had abundant granulated cytoplasm. There were also spindle cells which resembled endothelial cells (Figure 3). The conclusion was poorly differentiated malignant epithelial tumor from unknown origin, suspected from liver or mesothel, suggestive for IHC examination.

IHC staining was done as malignant pleomorphic epithelioid tumor, which is could be found in HCC, osteoclast like giant cell tumor of the pancreas, malignant mesothelioma, and choriocarcinoma. Choriocarcinoma could be excluded because there was no involvement of the tumors to the female genitalia organs. CK7, CK 19, glypican (GPC) 3, and CD10 staining were performed to ensure whether the tumor was pancreatic or liver origin. Vimentin and calretinin staining were performed to ensure whether the tumor was from mesothel.

IHC staining results: CK7/CK19, GPC 3, and CD10 were strongly positive; AFP was

moderately positive; vimentin, carcinoembryonic antigen (CEA), and calretinin were focally positive (Figure 4). The conclusion: tumor mass was reactive to specific markers that could be found in undifferentiated tumor. Tumor mass expressed epithelial markers from biliary, pancreas, ovary, and liver malignancy. However, histologically and location of the tumor were not appropriate with HCC. Based on histologic and IHC staining results, the possible diagnose was hepatoid carcinoma.

Patient came again to Cipto Mangunkusumo Hospital on March 2013 with a chief complaint of abdominal pain since five days before admission. Patient also experienced progressive abdominal enlargement, legs swelling, and dyspnea. Due to patient's terminal illness and poor condition, the therapy was only symptomatic and palliative care. Unfortunately, the patient's condition was getting worse and she died because of cachexia and sepsis on 22 March 2013.

DISCUSSION

HAC is a rare but highly aggressive tumor of uncertain origin. The clinical presentation of HAC may vary greatly depending on the anatomic location of the tumor. Usually patients with HAC present with lower abdominal pain and progressive abdominal distension.[6,7] In our case, the tumor was located in the retroperitoneal cavity and patient felt abdominal discomfort, pain, and enlargement. The tumor showed a relapse and progressed rapidly after the laparotomy surgery.

In addition to its rarity, HAC may be underdiagnosed because of the absence of unequivocal imaging features. Some CT characteristics have been identified as relatively common to HAC, whatever their localization. The primary tumor usually appears as a large, necrotic and moderately vascular mass; with the same density of the normal liver at baseline scan (the presence of necrotic areas often makes masses appear inhomogeneous). The tumor also moderately enhanced after intravenous iodinated contrast medium administration; invasion of adjacent anatomical landmarks, regional lymphadenopathies and distant metastases are frequently observed.[10-12]

In our case, USG and CT scan examinations showed a solid and inhomogeneous tumor mass in the peritoneal cavity. The tumor was locally invasive to the psoas muscle and there were enlargements of pelvic lymph nodes. However, there were no distant metastases and no significant abnormalities in other abdominals organ.

Grossly, the tumor may appear as entirely solid or with cystic areas and there may be multiple foci of hemorrhage and necrosis.[13]In our case, gross examination showed a few of solid and firm fragmented tissues. Microscopically, the tumor is composed mainly of large or polygonal cells with abundant eosinophilic cytoplasm and distinct cell border. Tumor cells arranged in sheets, solid or trabecular pattern, although it sometimes shows medullary proliferation.[13,14] We didn't found necrosis and hemorrhage area.

The tumor is composed of two closely related areas, hepatoid-like foci and adenocarcinomatous. Tumor cells in hepatoid foci resemble the morphology of HCC. The adenocarcinomatous component may be well or poorly differentiated, often with clear cells and papillary pattern with scattered large pleomorphic or multinucleated giant cells, which are indicative of fetal enteroblastic differentiation.[10,15,16]

There is no consensus for quantification of the proportion of hepatocellular differentiated component yet to accept as HAC. The proportion of hepatoid component ranges from 10 to 90% in reported cases of HAC. The glandular component frequently intermingles with the hepatoid component. The transition between glandular and hepatoid components of HAC can be gradual or abrupt.[17] In our case, the adenocarcinomatous component was not found. The tumor mostly composed of poorly differentiated tumor cells, arranged in solid and trabecular pattern.

Before a diagnosis of HAC is made, the metastases of a HCC should be ruled out. It is difficult to distinguish metastatic HCC from HAC. HAC occurs in patients with no history of hepatic disease, alcoholism or addiction to other potential sources of hepatic damage. Their livers demonstrate no functional or morphological abnormalities. Blood samples do not reveal elevated levels of hepatic enzymes, and imaging examinations fail to detect any major alteration as to volume and structure of the liver, except in the cases where hepatic metastases develop. If a liver specimen is obtained, normal features are demonstrated at pathology.[11-13]

In our case, there was no history of liver diseases (HbsAg serum test showed non-reactive result). There was also no evidence of an intrahepatic lesion in abdominal CT scan examination. Therefore, metastatic HCC was excluded.

Typically, an elevated level of serum AFP is detected in both HAC and HCC, although normal levels have also been reported. Most patients had elevated serum AFP (84.8%), with a range from less than 1.0 to 475.000 ng/mL.[3,13,14] In our case, patient's serum AFP was not elevated.

Elevation of serum CA-125, a marker for ovarian surface epithelial tumors would support an ovarian origin. Elevation of serum CA19-9, a marker for pancreas and biliary epithelial tumors would support a pancreas origin. Elevation of serum CEA, a marker for colon epithelial tumors would support a colon origin.[3,13,14] Patient's serum CA-125, CA 19-9, and CEA were normal. The results support that the tumor was retro-peritoneal origin and exclude any possible metastases tumor from other organs.

Immunohistochemically, many liver specific proteins, including AFP, alpha-1 antitrypsin (AAT), alpha-1 antichymotrypsin (ACT) and albumin (ALB) have been detected in the tumor cell cytoplasm. Of them, AFP is generally considered important for the diagnosis. The tumor is focally positive for polyclonal CEA (pCEA) and is positive for cytokeratin (CK). Focal positivity with CK 7 and CK 19 suggested the presence of a common epithelial adeno-carcinoma. CD10 and CEA positivity indicated canalicular differentiation and thus hepato-cellular origin.Recently, glypican 3 (GPC3) has been evaluated as a sensitive marker for AFP-producing gastric carcinoma and its hepatoid component. GPC3, a placental and hepatic surface heparin sulfate proteoglycan, expressed specifically in the fetal liver and malignant neoplasms of hepatocyte lineage.[10,13,14,17]

In our case, the tumor showed positivity in CK7 and CK 19 and support the epithelial origin. The positivity in AFP, GPC3, and CD10 support the hepatoid component. The CEA result was only focally positive. The result for vimentin was only focally positive, and it excluded mesenchymal tumor. The result for calretinin was also only focally positive, and it excluded mesothelioma as the differential diagnose.

Many cytogenetic and molecular studies had been undertaken to investigate patho-genesis and biological behavior of this variant. However, the histogenesis of HAC is still unclear. There are two possible origins of the tumor that have been hypothesized. Kishimoto et al and Akiyama et al proposed that adenocarcinomatous component of HAC might acquire hepatic differentiation during the tumor progression, "HAC transdifferentiation". Another possible origin, cancer arising from ectopic liver cells embedded in the organs where HAC develops and neoplastic transformation of persistent germ cells or of nonhepatic epithelium capable of multipotential differentiation.[12,17,18]

HAC commonly progresses rapidly, with metastases in the abdomen and occasionally to the lungs and the patients died within 1-2 years.[5,13] The reasons for the poor prognosis are not clearly understood. One possibility is that HAC produces AAT and/or ACT as well as AFP. AAT and ACT have immunosuppressive and protease-inhibitory properties that enhance invasiveness. Also, AFP has a suppressive effect on lymphocyte transformation. The other reasons for poor prognosis are that HAC has high proliferative activity, weak apoptosis and a rich neovascularization.[16,19]

HAC is treated like other adeno-carcinomas of the common type, depending on the organ system involved. Palliative chemo-therapy is the mainstay of treatment in non-operable, recurrent or metastatic cases. Most of HAC cases clinically appear to chemoresistant and curative resections are limited due to advanced lesions at diagnosis. One-year survival of 55% is reported with an overall median survival for HAC from any different primary organ of 11 months with a wide range depending on the primary tumor site.[11,17,19,20] In our case, patient died 1 year after laparotomy surgery without receiving any chemotherapy. Patient had relapse and only receiving palliative care because of poor condition and terminal stage of the disease.

SUMMARY

HAC is a rare variant of adenocarcino-ma with hepatic differentiation in both morphological and functional which occurs in extrahepatic organs. Although rare, this entity deserves wide recognition among pathologists and clinicians to avoid potential misdiagnosis and inappropriate therapy.

We report a case of HAC of the retroperitoneal cavity in a 56-year-old woman with clinical presentation of abdominal discomfort and enlargement. USG and CT scan examination shows inhomogeneous tumor mass in abdominal and pelvic cavity. The histological finding reveals malignant epithelial carcinoma with hepatoid foci. IHC staining may help in distinguishing HAC with other tumors. Serum AFP in HAC could be elevated, but it is normal in our patient. Factors that trigger differentiation towards a hepatoid morphology and production of AFP are still unknown.

HAC is an aggressive tumor with poor prognosis. Optimal management is still not well defined. Some literatures said that aggressive surgery followed by adjuvant chemotherapy may result in favorable outcome. Our patient died one year after laparotomy surgery without receiving any chemotherapy.

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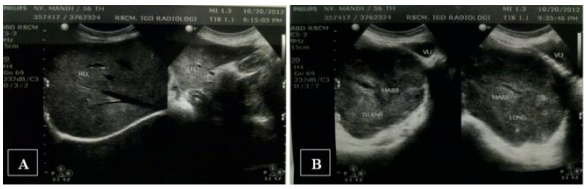

Figure 1. A. Pelvic USG showed a solid mass in the pelvic cavity. B. Abdominal USG showed normal liver.

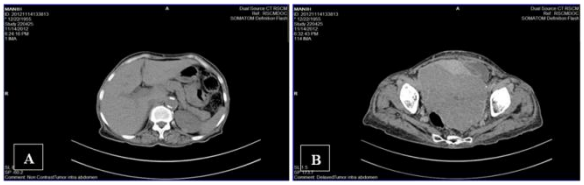

Figure 2. Abdominopelvic CT scan examination revealed an inhomogeneous mass in pelvic cavity (A) and normal liver (B).

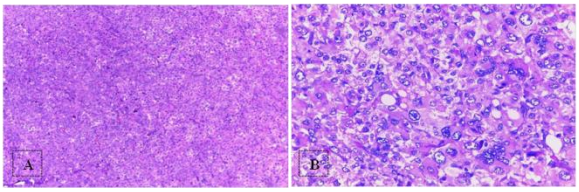

Figure 3. Hematoxylin eosin (HE) staining. (A) x100; (B) x400.

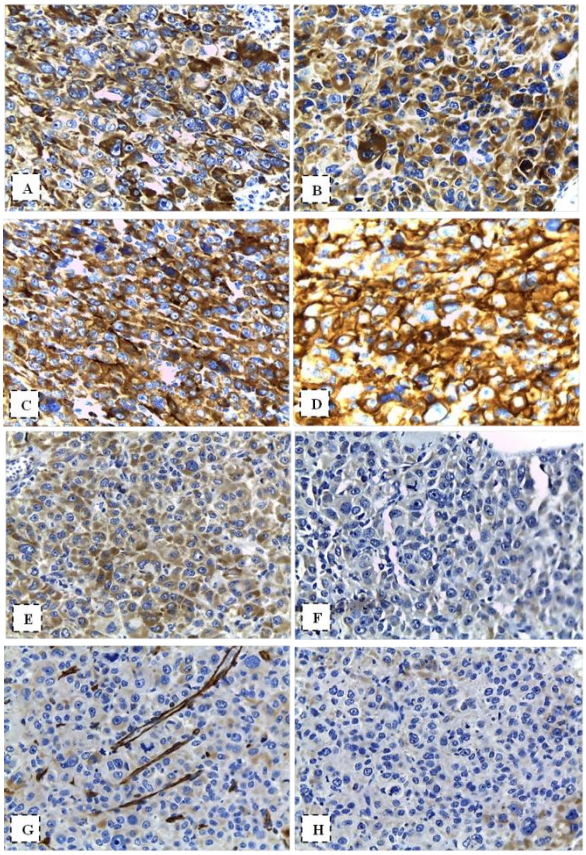

Figure 4. IHC staining. A. CK 7 (x400); B. CK 19 (x400); C. GPC3 (x400), and D. CD10 (x400) showed strongly positive results; E. AFP (x400) showed moderately positive result; F. CEA (x400); G. Vimentin (x400), and H. Calretinin (x400) showed only focally positive results.