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A Case of Metastatic Hepatocellular Carcinoma of the Ovary: An Immunohistochemical Study and Literature Review

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Hepatocellular carcinomas rarely metastasize to the ovaries. To our knowledge, only nine cases of metastatic hepatocellular carcinoma of the ovary have been reported in the literature. Here, we present an additional case in which an ovarian lesion was the initial presentation in a 43-year-old female patient. An exploratory laparotomy revealed a left ovarian solid mass measuring 6.5×4.0×3.5 cm, with a lobulated greenish brown sectioned surface. A subsequent ultrasonogram and CT scan revealed a concurrent hepatic mass, and laboratory tests showed high serum AFP and CA125 levels. Microscopically the tumor showed predominantly solid and trabecular patterns, and intercellular canaliculi containing bile pigments. A postoperative hepatic biopsy confirmed the hepatocellular carcinoma. The main differential diagnosis involved ovarian metastasis of the hepatocellular carcinoma, the hepatoid carcinoma of the ovary with liver metastasis, and a hepatoid yolk sac tumor. Diagnosis in such cases should be reached by careful clinical evaluation and a thorough pathologic examination accompanied by a histochemical and immunohistochemical work-up.

Key Words : Ovary; Hepatocellular carcinoma; Metastasis

The ovaries provide a fertile area for metastases and are the most commonly involved organs in the female genital tract, regardless of the location of the primary tumor.[1] The main primary sites are; stomach, kidney, breast, and colon.[2] However the spread of a hepatocellular carcinoma to the ovary is extremely rare, and may cause diagnostic problems. We have uncovered only nine documented cases, since the condition was first reported in an autopsy in 1983.[3-9] Here, we present an additional case in which the ovarian lesion was the initial presentation.

CASE REPORT

A 43-year-old female patient presented with lower abdominal pain for several months. A physical examination revealed a lower abdominal mass, but the liver was not palpable. An explolaparotomy revealed a left ovarian solid mass, measuring 6.5×4.0×3.5 cm, with a lobulated greenish brown cut surface. The right ovary was intact. Formalin fixation showed prominent green-colored areas suggestive of bile production (Fig. 1). A subsequent ultrasonogram and computed tomography (CT) scan revealed a hypodense hepatic mass (5.0 cm diameter) occupying the left lobe, associated with a 1 cm-sized daughter nodule in a cirrhotic background. Multiple metastatic foci were present in the abdominal and pelvic walls. Laboratory tests showed elevated levels of serum alpha-fetoprotein (AFP, 140 ng/mL), AST (47 U/L), ALT (99 U/L), CA125 (139 U/mL), and PIVKA2 (1,719 mAU/mL). A serologic test result for the hepatitis B virus was positive. Microscopically, the ovarian tumor resembled a hepatocellular carcinoma in terms of its architectural and cytological features, and solid and trabecular growth patterns were predominant. The tumor cells had moderate to abundant amounts of pale to eosinophilic cytoplasm. Nuclei appeared to be relatively uniform and had prominent nucleoli. Mitotic figures were often found, and bile was easily identified in intercellular canaliculi (Fig. 2). Immunohistochemically, the tumor cells stained positively for AFP, Cam5.2, hepatitis B core antigen (HBC Ag), and CD10, whereas immunoreactivities for hepatocyte-specific antigen, hepatitis B surface antigen (HBS Ag), CA125, and monoclonal carcinoembryonic antigen (mCEA) were absent. A postoperative hepatic needle biopsy confirmed a typical hepatocellular carcinoma.

The patient received aggressive postoperative chemotherapy, followed by transarterial embolization of the hepatic tumor. The patient remained alive at 5 months following surgery with elevated serum AFP levels, and is suspected to have a residual tumor.

DISCUSSION

Metastatic spread of hepatocellular carcinomas to the ovaries is unusual, and is often an incidental autopsy finding,[3] but a small number of such cases have been discovered while the patient is still alive.[4-9] All previous reports have shown elevated serum AFP levels and positive AFP staining, as was observed in this case. Moreover, in two previous cases, as in the present case, an ovarian tumor was discovered at the same time as a hepatic tumor.[5,7] In one case,[5] the hepatic tumor was detected on radiological investigation conducted after the ovarian tumor was removed. In the other cases, the ovarian metastases were noted after being diagnosed with a hepatic tumor. The tumors were usually bilateral and patients' ages varied from 31 to 68 years. Most cases were

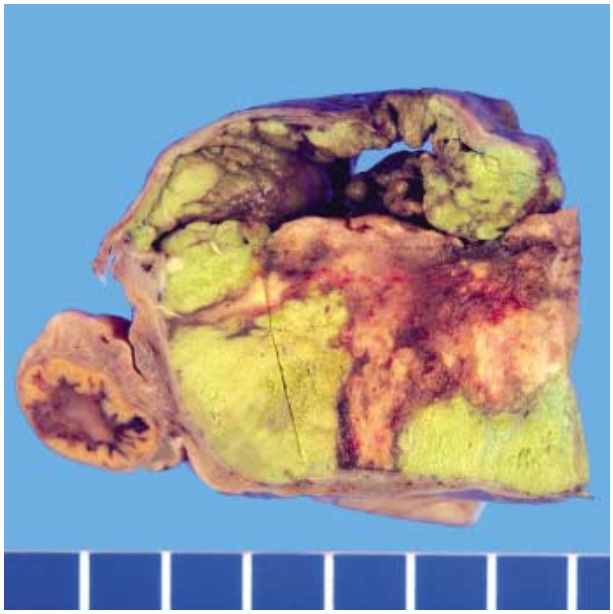

Fig. 1. Sectioned surface of a solid ovarian tumor showing a greenish nodular appearance with cystic, necrotic, and hemorrhagic changes.

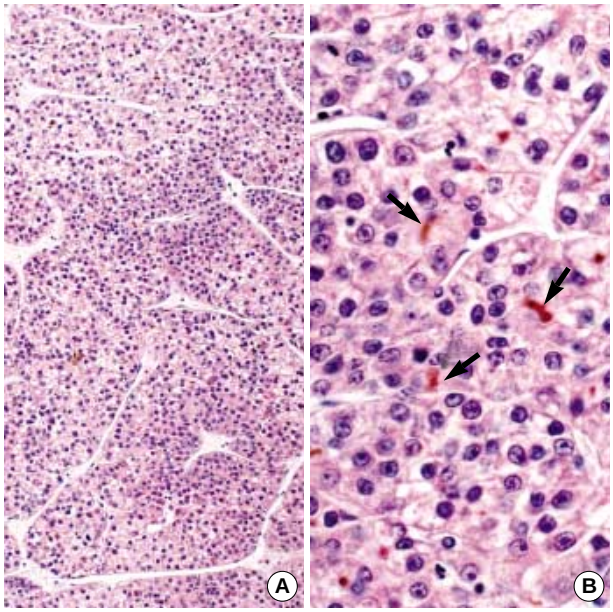

Fig. 2. The tumor shows diffuse sheets and a trabecular growth pattern (A). Tumor cells had abundant eosinophilic cytoplasm and intercellular canaliculi containing bile were observed (arrows) (B).

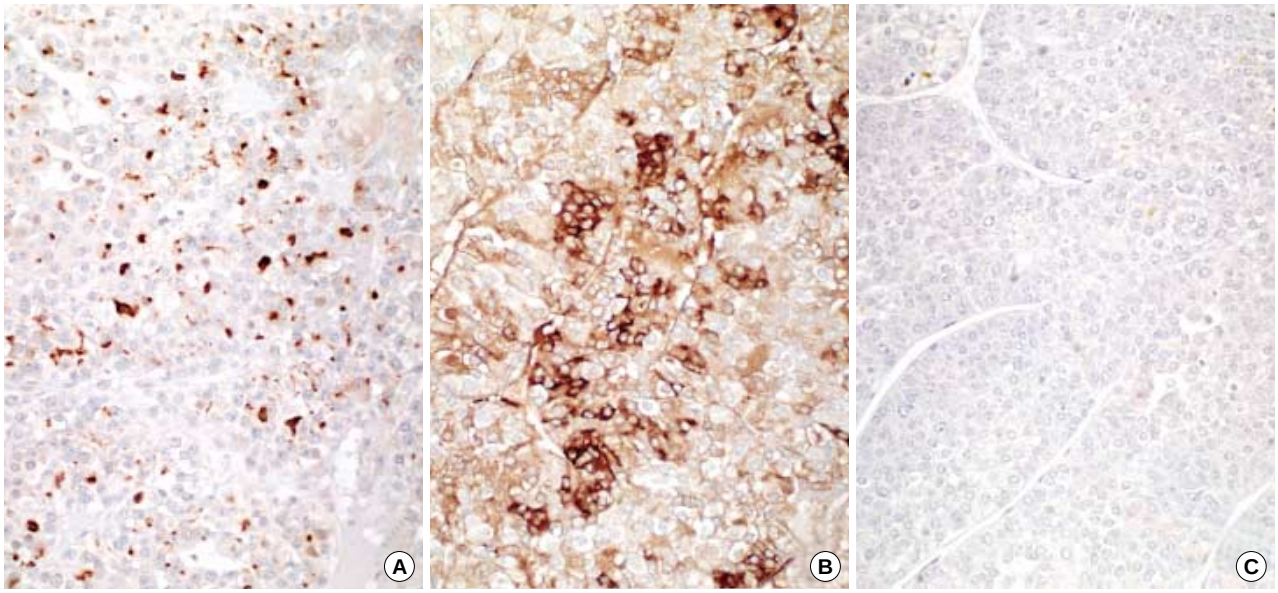

Fig. 3. Immunohistochemically, tumor cells showed canalicular staining for CD10 (A) and cytoplasmic reactivity for AFP (B), but negativity for mCEA (C).

accompanied by multiple metastases, e.g., in the lung, omentum, mesentery, and pelvic cavity. Tumor size varied widely, ranging from normal ovarian size to 15 cm in diameter. Grossly tumors showed mixed solid and cystic appearance in three cases, while the others were predominantly solid. The cystic component was frequently accompanied by necrosis and hemorrhage, and in two cases was yellow-green in color, which is compatible with bile pigmentation.[5,7] The present case showed a 6.5 cm-sized, predominantly solid ovarian tumor with a greenish brown cut surface.

Microscopic examination of previous cases showed diffuse solid and trabecular patterns with sinusoidal spaces characteristic of hepatocellular carcinomas. Tumor cells were polygonal with moderate to abundant pale eosinophilic cytoplasm and moderate to marked nuclear pleomorphism. Bile materials were seen in the canaliculi in two cases, and hyaline droplets were present in four, but were not seen in the present case. The histopathologic features of this case were similar to previously reported cases. Liver cell differentiation has been indicated by the immunohistochemical detection of AFP, hepatocyte-specific antigen, Cam5.2, CD 10, CK8/18, and viral markers.[10] In addition, among the reported cases, the absence of mCEA and CA125 supported a high possibility of hepatocellular carcinoma.[7,10] However, in the present case, hepatocyte-specific antigen was absent, whereas surprisingly, CD10 was present in the tumor cells. Therefore, the immunohistochemical pattern of AFP(+) and mCEA(-), accompanied by CD10(+) may be a specific marker for metastatic hepatocellular carcinoma of the ovary.

The main differential diagnosis of hepatocellular carcinoma metastatic to the ovary involves hepatoid yolk sac tumor,[11] and primary and metastatic hepatoid carcinoma of the ovary.[12] In the present case, a hepatoid yolk sac tumor was excluded since the patient was postmenopausal, and also due to the absence of typical foci of yolk sac tumor or any other germ cell element. However, it should be noted that a hepatoid yolk sac tumor may present with liver metastasis. Young *et al*.[5] concluded that the microscopic detection of canaliculi is more strongly suggestive of metastatic hepatocellular carcinoma than a hepatoid yolk sac tumor, and that bile can not be relied upon to distinguish metastatic hepatocellular carcinoma from hepatoid carcinoma.

Hepatoid carcinomas are a distinctive type of carcinoma that arises outside the liver but which resembles hepatocellular carcinoma both histologically and immunohistochemically.[5] The diagnosis of an ovarian hepatoid carcinoma should be based on the absence of clinical evidence of a hepatic tumor and the exclusion of other possible primary tumor sources. Although the cell origin of hepatoid carcinoma of the ovary remains controversial, a surface epithelial cell origin has been proposed.[13] Meanwhile hepatic phenotypes in hepatoid carcinoma have also been supported by the production of albumin, hepatic-type AFP, P-ConA, cytokeratin profile, and PIVKA-II.[14,15] Various studies have been performed to differentiate AFP producing tumors. Previous reports have indicated that immunohistochemical reactivity for CEA and CA125 supports a diagnosis of hepatoid carcinoma, whereas the presence of bile in an ovarian tumor favors a diagnosis of metastatic hepatocellular carcinoma.[7,13,14,16]

Here we present a case of a metastatic hepatocellular carcinoma of the ovary. The concurrent presence of hepatocellular carcinoma, canalicular bile pigment, and the immunohistochemical positivity of hepatocyte-related markers were found to be helpful diagnostic features. A specific marker suggestive of liver cell differentiation is desirable, because a correct diagnosis has important therapeutic and prognostic implications.

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