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Case Report

# Hepatoid carcinoma of the ovary: A case report and review of the literature

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ABSTRACT

Primary hepatoid carcinoma of the ovary (HCO) is a rare aggressive tumor that typically presents at an advanced stage in postmenopausal women with unilateral or bilateral ovarian masses and elevated AFP and CA125. We report a case of HCO in a 73 year-old woman who presented with abdominal distention, weight loss, and a large lower abdominal mass. Postoperative serum AFP was markedly elevated and trended down with initiation of chemotherapy. Review of the literature revealed thirty-two reported cases with no consensus on histogenesis or consistent immunohistochemical profile other than positive AFP staining in all but one case. Although the optimal treatment has not yet been determined, tumor debulking surgery followed by a platinum and taxane based chemotherapy regimen has shown promise. Both serum AFP and CA125 appear to have prognostic value and can be used to follow response to treatment and screen for recurrence.



## 1. Introduction

Extra-hepatic hepatoid carcinomas are a rare group of aggressive tumors with clinical and pathologic features that closely resemble hepatocellular carcinoma (HCC). They may arise in many areas outside of the liver including lungs, bladder, kidneys, uterus and ovaries, but most commonly in the stomach (Young et al., 1992; Su et al., 2013). Hepatoid carcinoma of the ovary (HCO) is reported mainly in post-menopausal women with unilateral or bilateral ovarian masses and elevated serum alpha-fetoprotein (AFP). Microscopically, these tumors demonstrate cells arranged predominantly in sheets and contain moderate to abundant amount of eosinophilic cytoplasm with pleomorphic nuclei (Lefkowitch, 1988). These tumors must be distinguished from metastatic HCC and other AFP-producing ovarian tumors including hepatoid yolk sac tumors (HYSTs), Sertoli–Leydig cell tumors, and dysgerminomas (Matsuta et al., 1991).

## 2. Case presentation

A 73 year-old gravida 3, para 2 was initially referred to her hematologist for anemia that was diagnosed during a prior hospital admission for Legionella pneumonia. Studies were consistent with a diagnosis of anemia of chronic disease and physical examination revealed a sizeable pelvic mass. The patient reported 60 lb weight loss and transient postmenopausal bleeding over the last year. CT of the abdomen and pelvis demonstrated a large pelvic mass with cystic and necrotic components measuring at least 18 cm by 17 cm with an additional 7 cm mass along the anterior peritoneal surface. Marked bladder compression and left-sided hydronephrosis were also present. No hepatic lesions were seen. Surgical exploration revealed a large, lobulated, necrotic mass originating from the left ovary (Fig. 1). The mass was densely adherent to the uterus and anterior abdominal wall, and had eroded into a portion of small bowel. Frozen section showed poorly differentiated carcinoma. Optimal cytoreductive surgery was performed including a total abdominal hysterectomy, bilateral salpingo-oophorectomy, and partial small bowel resection with reanastamosis. No gross residual disease was present. Final pathology showed a stage IIIC hepatoid carcinoma of the ovary.

Once a final histologic diagnosis was made, serum AFP was obtained and was markedly elevated at 2396 ng/mL (normal range 0–9) seven weeks after optimal cytoreduction. CT of the abdomen and pelvis at this time demonstrated new growth of a 4.7 cm nodular mass in the right upper quadrant separate from the liver and a 5.1 cm mass in the left side of the pelvis. AFP values rapidly decreased with initiation of chemotherapy (273 → 27 → 6 → 4 → 3). The patient completed six cycles of carboplatin (AUC of 6, every 3 weeks) and dose-dense paclitaxel (80 mg/m$^2$, every week) with appropriate dose reductions secondary to development of severe anemia and thrombocytopenia. She is currently doing well with no evidence of recurrence 26 months after surgery.

## 3. Pathology

Pathologic exam showed a 24 × 16.5 × 13 cm lobulated mass with tumor present on the outer surface. Cut section showed a tan yellow,

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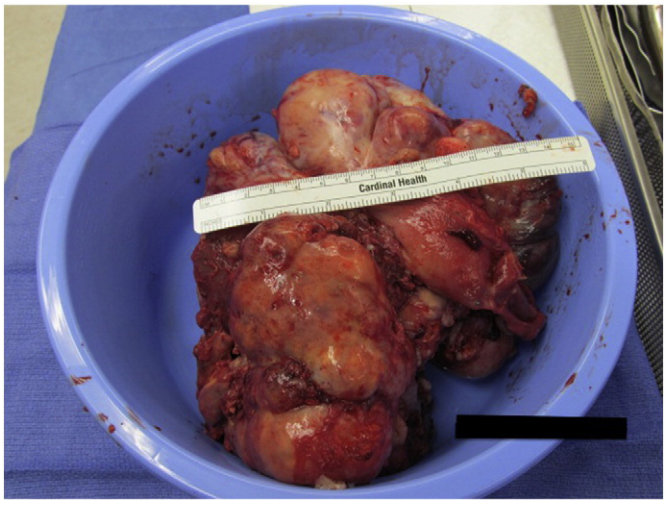


**Fig. 1.** Multi-lobate solid and cystic ovarian mass.

solid and cystic tumor which completely replaced the left ovary and fallopian tube. Microscopically, the tumor showed extensive patchy tumor necrosis with nests and sheets of polygonal cells, most with clear cytoplasm and some showing granular eosinophilic cytoplasm (Fig. 2). Nuclei were central, round to oval, and had distinct nucleoli. Occasional nuclei were markedly pleomorphic. Mitoses were 15 per 10 high power fields, with occasional atypical mitotic figures. Numerous PAS positive and alpha-fetoprotein (AFP) positive hyaline globules were scattered through the tumor (Fig. 2). In some areas fibrous bands traversed the tumor, lending a superficial resemblance to dysgerminoma. The tumor did not display the sinusoidal vascular pattern sometimes seen in both HCO and hepatocellular carcinoma.

Immunohistochemical studies were diffusely strong positive for AFP, keratin AE1/AE3, Arginase, and SALL-4, focally strong positive for HepPar1; focally positive for CEA and inhibin, and PLAP showed rare positive cells. Negative staining was observed for calretinin, EMA, OCT4, CK 7, CK 20, CD 30, CD99, and CD117.

## 4. Discussion

Primary hepatoid carcinoma of the ovary is a rare tumor that now has been reported in the literature thirty-two times since it was initially characterized in 1987 by Ishikura and Scully. The age range for patients is 35 to 78 years old with an average age of 56. The tumor was bilateral in seven (22%) of the reported cases and more than 75% of patients presented with stage III or IV disease. Rapid progression is also characteristic with a one and a two year survival rate of 83% and 53% respectively. The patient presented here has one of the largest reported HCO tumors to date measuring 25 cm in its greatest dimension (Table 1).

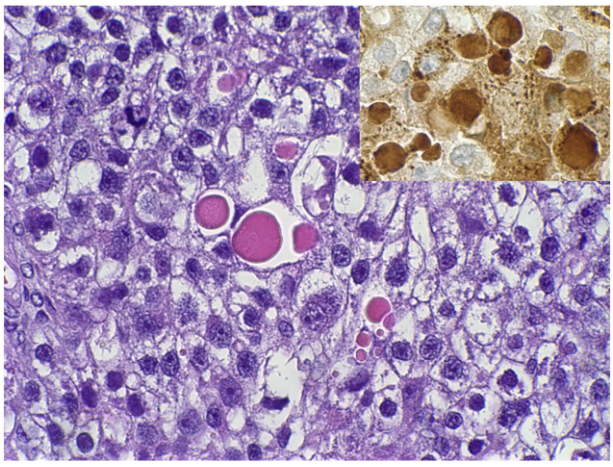

**Fig. 2.** Tumor cells are large and polygonal with cytoplasm ranging from pink and granular to clear. Nuclei are round to oval with distinct nucleoli. The cells resemble those of hepatocellular carcinoma. Large eosinophilic globules were scattered throughout the tumor. Immunostaining for AFP was strongly positive (upper right inset).

Immunohistochemical studies in this case showed SALL-4 positivity. SALL-4 is regarded as a marker for germ cell tumors and is negative in HCC, but has been found in hepatoid carcinomas from other sites (Ushiku et al., 2010). SALL-4 may prove useful in diagnosing HCO if additional cases also display the marker. Keratins AE1/AE3 were positive in this case, consistent with an epithelial origin for the tumor. However, CK 7 and CK 20, keratins often found in ovarian surface epithelial tumors, were negative. HCC is also usually negative for CK7 and CK20, which are sometimes used together to help identify carcinomas of unknown primary. Previous reported HCO cases varied when tested for CK7 and CK 20: 4 were CK7 positive, CK20 negative; three were CK7 negative, CK20 negative; and one was CK7 negative, CK20 positive (Table 2).

This tumor's unique pathologic appearance must be distinguished namely from HYSTs and metastatic HCC. HYSTs tend to occur in a younger age group (average age of 22 years), exhibit gonadal dysgenesis, and possess cellular uniformity with a lack of the giant bizzare cells with abundant cytoplasm (Trivedi et al., 1998). HCC must be excluded clinically and radiographically, as there is not yet any consistent pattern of ancillary lab studies to effectively rule it out. Additional studies will be required to see if SALL-4 will be a useful differential marker for HCC versus HCO.

The histogenesis of this tumor has also been controversial. Ishikura and Scully initially believed the tumor variant to be of surface epithelial origin and this view is supported by four reported cases of combined HCOs admixed with surface epithelial carcinomas- two serous, one mucinous, one endometrioid (Ishikura and Scully, 1987; Scurry et al., 1996; Tochigi et al., 2003). Additional support for this relationship is offered by the fact that HCOs and surface epithelial tumors tend to occur in the same age group. An AFP-producing serous papillary carcinoma in a 74 year-old woman has also been reported, although no hepatoid differentiation was present. Cancer antigen 125 (CA 125) is a non-specific marker that is usually seen in the serum and tumor tissue of patients with serous and endometrioid carcinomas yet serum CA 125 was elevated in 17 of 20 (85%) cases and staining was positive in 5 of 11 (45%) of the reported HCO cases. Furthermore, the abdominal cavity implants were serous papillary carcinoma following chemoradiation in Case 1 of Ishikura and Scully's case series of HCOs (Ishikura and Scully, 1987; Scurry et al., 1996).

A germ cell origin theory was alternatively proposed in 1988. The embryologic connection of the yolk sac to the primitive gut is the origin of the hepatobiliary primordium so it seems possible to have hepatoid cells in yolk sac tumors. However, it is counterintuitive to accept that surface coelomic epithelium behaves like liver when there is no obvious embryologic connection. An unlikely explanation would be surface coelomic tumors whose differentiation regressed back to germ cell origins that were then redirected toward hepatoid features (Lefkowitch, 1988). Only one case report to date has documented a HCO admixed with a sex cord stromal tumor of Sertoli-type (D'Antonio et al., 2010).

The best approach to treatment of this aggressive variant is also unknown. Most regimens reported in the literature are platinum and taxane based therapy similar to those recommended for common epithelial ovarian tumors. The patient we presented in this case responded very well to carboplatin and dose-dense paclitaxel. Of the 6 patients that were treated with carboplatin and paclitaxel, 5 reported survival outcomes and none were deceased at time of case publication: 100% 1 year survival rate (range 13–28 months). In one report, second-line treatment with sorafenib was initiated given its success as a first-line medication in the treatment of HCC, which pathologically resembles HCO. However, the tyrosine kinase inhibitor proved ineffective as AFP