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

Laura K. Randolph a,b, Maeve K. Hopkins b, Michael P. Hopkins a, Daniel A. Wasdahl c

a Department of Obstetrics and Gynecology, Aultman Hospital, Northeast Ohio Medical University, 2600 6th St. SW, Canton, OH 44708, United States
b Department of Obstetrics and Gynecology, Duke University Hospital, 2301 Erwin Rd, Durham, NC 27705, United States
c Department of Pathology, Aultman Hospital, Northeast Ohio Medical University, 2600 6th St. SW, Canton, OH 44708, United States

A R T I C L E   I N F O

Article history:
Received 9 April 2015
Received in revised form 9 June 2015
Accepted 16 June 2015
Available online 18 June 2015

Keywords:
Hepatoid ovarian carcinoma
Alpha-fetoprotein

A B S T R A C T

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.

© 2015 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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 post-menopausal 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/m², 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,
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, HepPar1; focally positive for CEA and inhibin, and PLAP showed rare positive cells. 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 CK20: 4 were CK7 positive, CK20 negative; three were CK7 negative, CK20 positive; 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 bizarre 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; Scully 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; Scully 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 (Lefkowitz, 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 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...
| Case | Age  | Site/size (cm) | Stage | AFP  | CA125 | Post-operative treatment                                                                                      | Outcome          | Reference                      |
|------|------|----------------|-------|------|-------|-------------------------------------------------------------------------------------------------------------|-------------------|-------------------------------|
| 1    | 42   | L 6.4; R 5.4   | IIB   | ND   | ND    | Chemoradiation                                                                                              | Died (5 years)    | Ishikura and Scully (1987)    |
| 2    | 71   | L 20           | IIIC  | ND   | ND    | Radiation                                                                                                   | Alive (2 years)   | Ishikura and Scully (1987)    |
| 3    | 57   | R 10.5 × 7.5 × 5.5 | IIIC | ND   | ND    | Chemoradiation                                                                                              | Died (4 months)   | Ishikura and Scully (1987)    |
| 4    | 78   | ND             | IIIC  | ND   | ND    | Melphalan                                                                                                   | Died (8 months)   | Ishikura and Scully (1987)    |
| 5    | 68   | R 10 × 6 × 5   | IIIC  | ND   | ND    | Chemoradiation                                                                                              | Died (10 months)  | Ishikura and Scully (1987)    |
| 6    | 64   | R 18 × 17 × 16 | IA    | 23,170 | 58 | IP cisplatin; chemotherapy                                                                                   | Alive (2 years)   | Matsuta et al. (1991)         |
| 7    | 62   | R 8.2 × 7.8 × 6.4 | IA   | 2450 | ND    | Bleomycin/vinblastine/cisplatin; cisplatin/etoposide; cyclophosphamide/mitomycin/5-fluorouracil              | Died (13 months)  | Tamakoshi et al. (1993)       |
| 8    | 52   | ND             | III   | 2500 | Elevated | Carboplatin/cyclophosphamide/cisplatin; bleomycin/vinblastine/cisplatin; cisplatin/etoposide; paclitaxel | Recurred (7 months) | Badreddine et al. (1993)      |
| 9    | 43   | L 6 × 7; R 6 × 8 | IIIC  | 74   | 158   | Cisplatin/epirubicin/ifosfamide                                                                               | Alive (2 years)   | Nishida et al. (1995)         |
| 10   | 72   | L 9.5; R 8.5   | ND    | 802  | ND    | Carboplatin                                                                                                 | Recurred (6 months) | Scurry et al. (1996)          |
| 11   | 35   | L 35 × 30      | IIIA  | 358  | Normal | Cyclophosphamide/cisplatin/carboplatin/etoposide; paclitaxel                                               | Died (12 months)  | Trivedi et al. (1998)         |
| 12   | 53   | L 9 × 8 × 6     | III   | 250  | ND    | Cisplatin/cyclophosphamide                                                                                   | Died (20 months)  | Senzaki et al. (1999)         |
| 13   | 61   | L 12 × 9       | III   | 73,080 | 80 | IP cisplatin; cisplatin/5-fluorouracil/etoposide                                                          | Died (18 months/22 months) | Badreddine et al. (1993)      |
| 14   | 64   | R 23 × 17 × 16 | IA    | 900  | 53    | Cisplatin/cyclophosphamide; cisplatin/paclitaxel/radiation; cisplatin/paclitaxel                            | Recurred/died (18 months/5 years) | Lee et al. (2002)             |
| 15   | 36   | L 10 × 8 × 8    | IIIIC | 888  | ND    | Patient declined                                                                                             | ND               | Watanabe et al. (2003)        |
| 16   | 69   | L 12           | IA    | 590  | 11    | Patient declined                                                                                             | ND               | Tochigi et al. (2003)         |
| 17   | 53   | L 10           | IIB   | 257,522 | Normal | Carboplatin/paclitaxel                                                                                       | Alive (13 months) | Tochigi et al. (2003)         |
| 18   | 76   | L 16           | IIB   | 24,000 | ND   | None                                                                                                        | Alive (4 years)   | Tochigi et al. (2003)         |
| 19   | 57   | R 13 × 9 × 8    | ND    | 24,879 | ND   | None                                                                                                        | Alive (3 years)   | Tsung and Yang (2004)         |
| 20   | 63   | R 16 × 12      | IA    | 454  | 85    | Cisplatin/cyclophosphamide                                                                                   | Alive (7 months)  | Yigit et al. (2006)           |
| 21   | 40   | R 11 × 9.5 × 3  | III   | 32,338 | 1297 | Chemotherapy                                                                                                 | Alive (6 months)  | Kwon et al. (2006)            |
| 22   | 42   | R 17 × 6       | IA    | 600  | ND    | Carboplatin/paclitaxel                                                                                       | Died (16 months)  | Lazaro et al. (2007)          |
| 23   | 50   | L 10 × 8; R 7 × 6 | IIIIC | 2    | 538   | Cisplatin/paclitaxel; cisplatin/gemcitabine; doxorubicin                                                   | Died (2 years)    | Ozan et al. (2008)            |
| 24   | 65   | R 12 × 10 × 6   | III   | 329,732 | 402 | Cisplatin/paclitaxel                                                                                         | ND               | Gonzalez et al. (2008)        |
| 25   | 42   | L 11 × 7 × 7    | ND    | 70   | ND    | Patient declined                                                                                             | ND               | Zizi-Sermetzoglou et al. (2009) |
| 26   | 34   | R 14 × 10.5 × 8 | IIA   | Normal | Normal | Carboplatin/paclitaxel                                                                                       | ND               | Sun et al. (2009)             |
| 27   | 42   | L 6 × 4 × 3     | I     | ND   | ND    | Chemoradiation following recurrence                                                                         | ND               | D’Antonio et al. (2010)       |
| 28   | 46   | L 4.5; R 8.5    | III   | -30,000 | 414 | Carboplatin/paclitaxel; sorafenib                                                                            | ND               | Pandey and Truica (2011)      |
| 29   | 55   | L 11 × 7 × 7    | IIIIC | 249  | 168   | Intraop IP nitrogen mustard; docetaxel/nedaplatin                                                           | Alive (10 months) | Liu et al. (2012)             |
| 30   | 53   | L 7 × 7 × 6; R 9 × 7 × 6 | IIIIC | 761 | 125 | Carboplatin/paclitaxel                                                                                       | Alive (15 months) | Campos et al. (2013)          |
| 31   | 57   | ND 12 × 12 × 12 | IIIIC | 397  | 1247 | Intraop IP paclitaxel; carboplatin/paclitaxel; radiation (lumbar metastasis)                              | Alive (28 months) | Wang et al. (2013)            |
| 32   | 73   | L 25 × 17 × 13  | IIIIC | 2396 | ND   | Carboplatin/paclitaxel                                                                                       | Alive (26 months) | Present case                  |
levels increased and a new tumor metastasis was noted in the liver prior to discontinuation of the medication (Pandey and Truica, 2011). A few cases have included intraperitoneal chemotherapy and radiation as well, but there is insufficient data to effectively compare and recommend treatment options.

5. Conclusion

Neither the histogenesis nor a consistent immunohistochemical profile of HCO has been established, however AFP staining is consistently positive with only one reported exception. Both AFP and CA125 appear to have prognostic value and can be used to follow response to treatment and screen for recurrence. Treatment regimens have varied, but optimal cytoreductive surgery followed by a platinum and taxane based chemotherapy regimen has demonstrated outcomes similar to that seen with other ovarian carcinomas.

Table 2

| Stain         | N | Positive | %  |
|---------------|---|----------|----|
| AFP           | 29| 28       | 97 |
| Mucin         | 7 | 7        | 29 |
| Glycogen      | 8 | 1        | 13 |
| Albumin       | 10| 10       | 100|
| α-1 antitrypsin| 11| 9        | 82 |
| α-1 chymotrypsin| 7 | 7        | 100|
| CEA           | 13| 8        | 62 |
| mCEA          | 4 | 2        | 50 |
| pCEA          | 6 | 5        | 83 |
| Bile          | 10| 5        | 50 |
| CA-125        | 11| 5        | 45 |
| hCG           | 11| 1        | 9 |
| hPL           | 6 | 0        | 0 |
| EMA           | 6 | 4        | 67 |
| CK7           | 9 | 6        | 67 |
| CK8           | 2 | 2        | 100|
| CK18          | 7 | 6        | 86 |
| CK20          | 9 | 2        | 22 |
| Hep Par 1     | 7 | 6        | 86 |
| CD10          | 4 | 1        | 25 |
| Inhibin       | 7 | 2        | 29 |
| OCT 3/4       | 3 | 0        | 0 |
| Vimentin      | 3 | 0        | 0 |
| Calretinin    | 2 | 0        | 0 |
| CD40          | 2 | 0        | 0 |
| PLAP          | 2 | 0        | 0 |

* Uterine metastasis was weakly positive for AFP in the sole case of AFP negative staining in the primary HCO tumor.

D’Antonio, A., De Dominicis, G., Addesso, M.,CALEO, A., Boscaino, A., 2010. Hepatic carcinoma of the ovary with sex cord stromal tumor: a previously unrecognized association. Arch. Gynecol. Obstet. 281, 765–768.

Gonzalez, E.T., Arguelles, M., Jimenez-Heffernan, J.A., Dhimes, P., Vicandi, B., Pinedo, F., 2008. Cytologic features of hepatic carcinoma of the ovary: a case report with immunocyto logic evaluation of HepPar1 Acta Cytol. 52, 490–494.

Ishikura, H., Scully, R., E., 1987. Hepatic carcinoma of the ovary. A newly described tumor. Cancer 60, 2775–2784.

Kwon, J.E., Kim, S.H., Cho, N.H., 2006. No ancillary finding is valid to distinguish a primary ovarian hepatic carcinoma from metastatic hepatocellular carcinoma. Int. J. Gynecol. Cancer. 16, 1601–1604.

Lazaro, et al., 2007. Hepatic carcinoma of the ovary and management. Acta Obstet. Gynecol. 86, 498–505.

Lee, C.H., Huang, K.G., Ueng, S.H., Swei, H., Chueh, H.Y., Lai, C.H., 2002. A hepatic carcinoma of the ovary. Acta Obstet. Gynecol. Scand. 81, 1080–1082.

Leffkowitch, J.H., 1988. Liver look-alike: hepatic ovarian carcinoma. Hepatology 8 (5), 1168–1169.

Liu, X., Wang, X., Zhu, F., 2012. Hepatic carcinoma of the ovary: a case report and review of the literature. Oncol. Lett. 4, 947–950.

Matsuta, M., Ishikura, H., Murakami, K., Kagabu, T., Nishiya, I., 1991. Hepatic carcinoma of the ovary: a case report. Int. J. Gynecol. Pathol. 10, 302–310.

Maymon, E., Fiuza, B., Mazor, M., Bashiri, A., Silberstein, T., Yanai-Inbar, I., 1998. Primary hepatic carcinoma of the ovary in pregnancy. Am. J. Obstet. Gynecol. 179, 820–822.

Nishida, T., Sugiyama, T., Katoaka, A., Ushijima, K., Ota, S., Iwanzaga, S., Yaskushi, M., 1995. Ovarian hepatic carcinoma without staining for alpha-fetoprotein in the primary site. Int. J. Gynecol. Cancer 5, 314–318.

Ozan, H., Nazhholu, H., Oztas, S., 2008. A case of hepatic carcinoma of the ovary. Eur. J. Gynaecol. Oncol. 5, 556–557.

Pandey, M., Truica, C., 2011. Hepatic carcinoma of the ovary. J. Clin. Oncol. 29, 446–448.

Scorry, J.R., Brown, R.W., Jobjing, T., 1996. Combined ovarian serous papillary and hepatic carcinoma. Gynecol. Oncol. 63, 138–142.

Senzaki, H., Kiyozuka, Y., Mizouza, H., et al., 1989. An autopsy case of hepatic carcinoma of the ovary. Eur. J. Gynaecol. Oncol. 5, 556–557.

Wang, et al., 2013. Clinical and pathological features of hepatic carcinoma of the ovary: a case report. World J. Surg. Oncol. 11, 29.