

Granulosa cell tumor and ovarian hepatoid carcinoma as a collision tumor

Surang Triratanachat*

Somchai Niruthisard* Prasert Trivijitsilp*

Triratanachat S, Niruthisard S, Trivijitsilp P. Granulosa cell tumor and ovarian hepatoid carcinoma as a collision tumor. Chula Med J 2004 Feb; 48(2): 101 - 9

Hepatoid carcinoma in the ovary has been recently described. It has been reported to arise novo in the ovary or in association with epithelial-stromal carcinoma. A case of 58-year-old woman with both granulosa cell tumor and hepatoid carcinoma, arranged as collision tumor in the left ovary is herein presented. Both components showed positive staining for alpha-fetoprotein (AFP).

Keywords: *Hepatoid carcinoma, Granulosa cell tumor, Collision tumor, AFP.*

Reprint request : Triratanachat S, Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.

Received for publication. March 15, 2004.

สุรางค์ ตริรัตน์ชาติ, สมชัย นิรุตติศาสตร์, ประเสริฐ ตริวิจิตรศิลป์. มะเร็งรังไข่ชนิด hepatoid และ granulosa cell ซึ่งเกิดขึ้นร่วมกัน. จุฬาลงกรณ์เวชสาร 2547 ก.พ; 48(2): 101 - 9

มีรายงานว่าพบมะเร็งชนิด hepatoid ที่รังไข่ได้ไม่บ่อยนัก โดยอาจพบชนิดเดียวหรือร่วมกับ มะเร็งรังไข่ชนิด epithelial-stromal ก็ได้ ในรายนี้พบในผู้ป่วยอายุ 58 ปี เป็นมะเร็งรังไข่ข้างซ้าย ชนิด hepatoid ร่วมกับ granulosa cell ซึ่งทั้งสองชนิดย่อยผลิต alphafetaprotein (AFP)

In 1986, Ishikura et al. reported seven cases of gastric adenocarcinoma with hepatoid foci that were immunoreactive for alpha-fetoprotein (AFP); hence, they proposed the term "hepatoid adenocarcinoma" for it. ⁽¹⁾ Subsequently, hepatoid carcinoma had been reported in several extragenital organs such as the lung ⁽²⁾, renal pelvis⁽³⁾, papillar of Vater ⁽⁴⁾ and urinary bladder.⁽⁵⁾ In the female genital tract, in particular, hepatoid carcinoma was firstly described in the ovary by Ishikura and Scully in 1987.⁽⁶⁾ To the best of our knowledge, there are 15 cases of pure hepatoid carcinoma of the ovary ⁽⁶⁻¹⁵⁾ and 4 cases of ovarian hepatoid carcinoma combined with epithelial-stromal carcinoma ⁽¹⁶⁻¹⁷⁾ that were reported in literature. Hepatoid carcinoma also occurred in the endometrium ⁽¹⁸⁾ and fallopian tube.⁽¹⁹⁾ Herein, we present a case of ovarian carcinoma composed of granulosa cell tumor and hepatoid carcinoma, as a collision tumor.

Case report

A 58-year-old woman, gravida 3, presented with postmenopausal bleeding and a progressively enlarging pelvic mass. Her pelvic examination and ultrasonography revealed a large solid ovarian tumor with no evidence of any other intraabdominal mass. Her physical examination and routine laboratory data were within normal limits. A laparotomy was performed which discovered a left ovarian tumor of 25 x 20 cm in size with no extraovarian extension. A total abdominal hysterectomy with bilateral salpingo-oophorectomy and appendectomy was performed. The postoperative course was uneventful and the patient received adjuvant chemotherapy.

Gross pathology

The left ovary was replaced by a mass of 25 x 20 cm, a solid tumor with smooth external surface. Sectioning showed a tan solid cut surface with extensive necrosis and cystification. A distinct grayish white, well defined nodule measuring 5 x 3 cm was noted at one edge of the main mass. The left fallopian tube and right adnexa were grossly unremarkable with an endometrial cavity containing an endometrial polyp, 2 x 1 x 1 cm.

Microscopic findings

The tumor had two different components. The main component represented hepatoid carcinoma which consisted of uniform neoplastic cells arranged in sheets with glandular formation (Figure 1,2). The tumor cells were large polygonal with abundant eosinophilic cytoplasm and had round vesicular with prominent nucleoli (Figure 3). Occasionally, bizarre giant cells were identified, scattered throughout the tumor. PAS-positive diastase resistant hyaline globules were found in some cells. Smaller but well circumscribed peripheral nodules were composed of tumor cells with both diffuse and trabecular arrangement in fibromatous background stroma (Figure 4). Call-Exner bodies were occasionally seen. The tumor cells had unapparent cytoplasm, with frequently found nuclear grooves and rather uniform nuclei with rare mitoses (Figure 5).

Histochemical stain for mucicarmine was negative in both components. Immunohistochemical stain for alpha-fetoprotein (AFP) was diffusely strong in hepatoid carcinoma (Figure 6), but diffusely weak

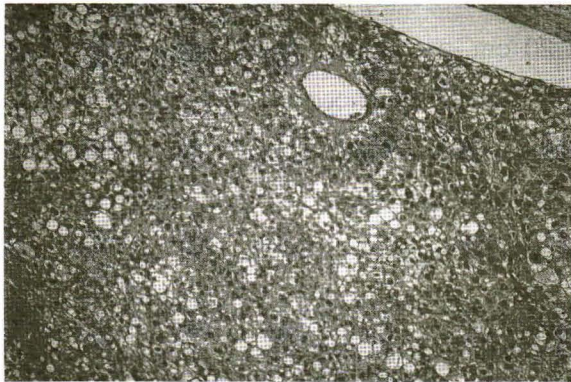


Figure 1. Hepatoid carcinoma arranging in sheets.
(Hematoxylin-eosin, x 100)



Figure 2. Hepatoid carcinoma arranging in glands.
(Hematoxylin-eosin, x 100)

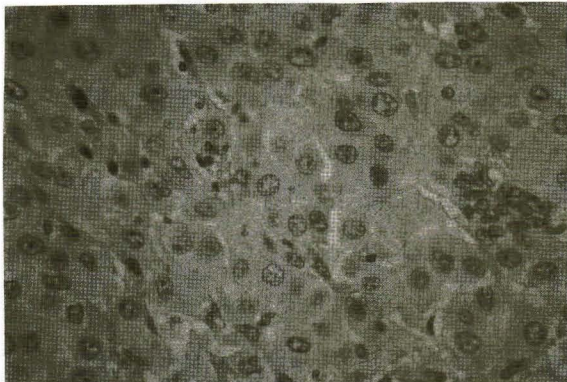


Figure 3. Hepatoid carcinoma cells disclose large polygonal shape with abundant eosinophilic cytoplasm and round vesicular nuclei with prominent nucleoli (Hematoxylin-eosin, x 400)



Figure 4. Granulosa cell tumor component discloses trabecular arrangement in fibromatous background stroma. (Hematoxylin-eosin, x 40)

in the granulosa component. The hepatoid carcinoma part also disclosed diffusely weak immunoreactivity for low molecular weight keratin, carcinoembryonic antigen (CEA) and focally weak staining for epithelial membrane antigen (EMA), whilst all of these antibodies revealed negative results in granulosa cell tumor. The granulosa component was diffusely stained for inhibin (Figure 7).

Discussion

Hepatoid carcinoma has recently been described as a distinctive type of carcinoma that arises outside the liver but resembles hepatocellular carcinoma both histologically and immunohistologically. It has been reported in several extragenital organs such as the stomach⁽²⁰⁾, lung⁽²⁾, kidney, genital tract, it also occurred in the endometrium⁽¹⁸⁾, the

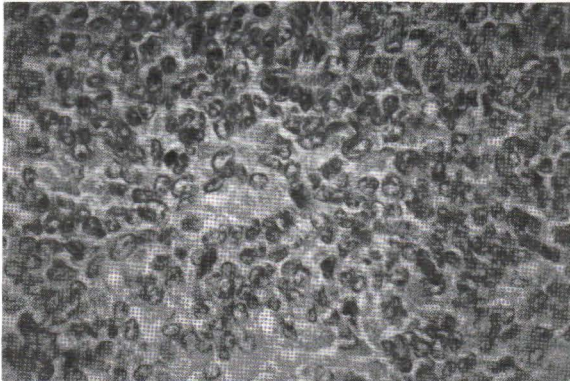


Figure 5. Granulosa tumor cells have inapparent cytoplasm, frequent nuclear grooves (arrow) and rather uniform nuclei with rare mitoses (Hematoxylin-eosin, x 400)

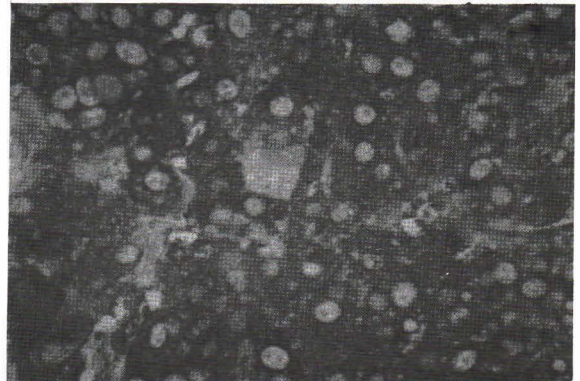


Figure 6. Immunohistochemical stain for alpha-fetoprotein (AFP) was diffusely strong in cytoplasm of hepatoid carcinoma (Alpha-fetoprotein, x 400)

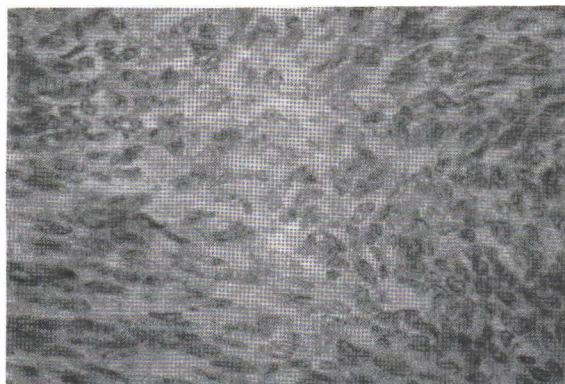


Figure 7. Granulosa component was stained for inhibin (Inhibin, x 400)

fallopian tube and particularly in the ovary which Ishikura and Scully firstly described in 1987.⁽⁶⁾ This case is the ovarian hepatoid carcinoma, occurred with granulosa cell tumor as a collision tumor.

Although the ovary is monodermal in origin, some neoplasms are able to differentiate into endodermal type of tissue such as liver cells⁽²¹⁾ and enteric-like glands.⁽²²⁾ Hepatic differentiation has been reported in association with germ cells⁽²²⁾, common

epithelial⁽¹⁶⁾, and sex cord stromal tumors.⁽²³⁻²⁴⁾ This supports the neometaplastic theory which explains that alteration of neoplastic cells into cells of different types not normally found in the tissue of origin is possible.⁽²³⁾ According to Ishikura and Scully,⁽⁶⁾ hepatoid carcinoma is most likely a variant of the common epithelial carcinoma since they are both found in the same age group and there is evidence that it can occur in association with serous papillary carcinoma.⁽¹⁶⁾ It is

unlikely to belong to the germ cell origin because of the unusual age group,⁽⁶⁾ and inability to find any pattern of germ cell tumors.⁽⁷⁾

The microscopic finding of hepatoid carcinoma in previous case reports as well as in this case are the same. Most of the tumors were arranged in solid sheets with some glandular formation^(6,8,16) but they also have other patterns such as anastomosing trabeculae, cords⁽⁶⁾ or pseudopapillary features.⁽⁶⁾ The neoplastic cells have moderate to abundant eosinophilic cytoplasm with central nuclei and distinct cellular border. The majority of the cells are uniform in size and shape, but occasional giant cells with some multinucleation are also observed.⁽⁶⁾ To the best of our knowledge, there are 19 previously reported cases of ovarian hepatoid carcinoma,^(6-10,16) so far this is the first case of collision tumor between hepatoid carcinoma and granulosa cell tumor.

The immunohistochemical study for AFP in hepatoid carcinoma of the ovary in the literature showed positive results^(6,16) except one case.⁽⁸⁾ In our case, the hepatoid component disclosed diffusely strong immunoreactivity for AFP which might exist.

Keratin immunoreactivity was not reported in any previous case of ovarian hepatoid carcinoma. However in other organs, the tumor usually stained for low molecular weight keratin^(5,19) like in this case. While keratin staining in granulosa cell tumor variably shows immunoreactivity from 20 % - 68 % for monoclonal cytokeratin antibodies.⁽²⁵⁻²⁸⁾ The detection of cytokeratins in normal granulosa cells is of interest in view of their disputed histogenesis. Whereas many embryologists favor the ultimate origin of granulosa cells from coelomic epithelium of the genital ridge, others believe they derive from gonadal mesenchyme.⁽²⁸⁾ The detection of cytokeratin,

desmosomes and tonofilaments in human granulosa cells is strong evidence in favor of their epithelial nature. However, it is not possible to deduce whether it originates from surface epithelium or from a precursor mesenchymal cell⁽²⁹⁾ which transform into a cytokeratin expressing cell, as has been proposed in the development of renal tubular epithelium⁽³⁰⁾ and in mesothelium.⁽³¹⁾ Interestingly, in this case the granulosa cell tumor occurred with hepatoid carcinoma which is supposed to have derived from the epithelial surface of the ovary.

Inhibin is a glycoprotein produced from granulosa cell of the ovary⁽³²⁾ which has recently been proved a sensitive tumor marker for adult granulosa cell tumors. In our case, the granulosa component showed diffusely strong immunoreactivity for this antibody.

Considering the hepatoid carcinoma as a primary ovarian tumor, we have to exclude this tumor from metastatic hepatocellular carcinoma of metastatic hepatoid carcinoma from other organs e.g. the stomach⁽²⁰⁾, lung⁽²⁾, bladder⁽⁵⁾ and renal pelvis.⁽³⁾ Other differential diagnoses are several primary ovarian tumors with hepatoid differentiation such as hepatoid yolk sac tumors, Sertoli-Leydig tumors with heterologous differentiation⁽²¹⁾ and granulosa cell tumors with hepatic differentiation.⁽²²⁾ In the present case, both investigation and microscopic findings help us exclude the above tumors.

Although in our case, there is a short follow-up information (18 months) and the patient still has uneventful course, the biological behavior of ovarian hepatoid carcinoma has been reported to be aggressive. In conclusion, we presented a rare collision tumor of hepatoid carcinoma and granulosa cell tumor which were both immunoreactive for AFP.

References

1. Ishikura H, Fukasawa Y, Ogasawara K, Natori T, Tsukada Y, Aizawa M. An AFP-producing gastric carcinoma with features of hepatic differentiation. A case report. *Cancer* 1985 Aug 15; 56(4): 840 - 8
2. Ishikura H, Kanda M, Ito M, Nosaka K, Mizuno K. Hepatoid adenocarcinoma : a distinctive histological subtype of alpha-fetoprotein-producing lung carcinoma. *Virchows Arch A Pathol Anat Histopathol* 1990; 417(1):73 - 80
3. Ishikura H, Ishiguno T, Enatsu C, Fujii H, Kakuta Y, Kanda M, Yoshiki T. Hepatoid adenocarcinoma of the renal pelvis producing alpha-fetoprotein of hepatic type and bile pigment. *Cancer* 1991 Jun 15; 67(12): 3051 - 6
4. Gardiner GW, Lajoie G, Keith R. Hepatoid adenocarcinoma of the papilla of Vater. *Histopathology* 1992 Jun; 20(6): 541 - 4
5. Sinard J, Macleay JR, Melamed J. Hepatoid adenocarcinoma in the urinary bladder. Unusual localization of a newly recognized tumor type. *Cancer* 1994 Apr 1; 73(7): 1919 - 25
6. Ishikura H, Scully RE. Hepatoid carcinoma of ovary. A newly described tumor. *Cancer* 1987 Dec 1; 60(11): 2775 - 84
7. Matsuta M, Ishikura H, Murakami K, Kagabu T, Nishiya I. Hepatoid carcinoma of the ovary: A case report. *Int J Gynecol Pathol* 1991; 10(3): 302 - 10
8. Nishida T, Sugiyama T, Kataoka A, Ushijima K, Ota S, Inanaga S, Yakushiji M. Ovarian hepatoid carcinoma without staining for alpha-fetoprotein in the primary site. *Int J Gynecol Cancer* 1995 Jul; 5(4): 314 - 8
9. Badreddine J, Rabouille Y, Heron JF, Mandard AM. Ovarian tumor with hepatoid differentiation: Discussion and review of the literature. Report of a case. *Ann Pathol* 1993; 13(1): 37 - 9
10. Tamakoshi K, Horio J, Okamoto T, Sakakibara K, Hottdic S. A case report of hepatoid carcinoma of the ovary. *Nippon Sanka Fujinka Gakki Zasshi* 1993 May;45(5):479-81
11. Trivedi D, Dave K, Shah M, Karelia N, Patel D, Wadhwa M. Hepatoid carcinoma of the ovary— a case report. *Eur J Gynecol Oncol* 1998; 19(2): 167 - 9
12. Maymon E, Piura B, Mazor M, Bashiri A, Silberstein T, Yanai-Inbar I. Primary hepatoid carcinoma of ovary in pregnancy. *Am J Obstet Gynecol* 1998 Sep; 179(3 pt 1): 820 - 2
13. Senzaki H, Kiyozuka Y, Mizuoka H, Yamamoto D, Ueda S, Izumi H, Tsubura A. An autopsy case of hepatoid carcinoma of the ovary with PIVKA-II production: immunohistochemical study and literature review. *Pathol Int* 1999 Feb; 49(2): 164 - 9
14. Lee CH, Huang KG, Ueng SH, Swei H, Chueh HY, Lai CH. A hepatoid carcinoma of the ovary. *Acta Obstet Gynecol Scand* 2002 Nov; 81(11): 1080 - 2
15. Watanebe Y, Umemoto M, Ueda H, Nakai H, Hoshiai H, Noda K. Cytopathologic and clinicopathologic features of ovarian hepatoid carcinoma. A case report. *Acta Cytol* 2003 Jan-Feb;47(1): 78 - 82
16. Scurry JP, Brown RW, Jobling T. Combined ovarian serous papillary and hepatoid

- carcinoma. *Gynecol Oncol* 1996 Oct; 63(1): 138 - 42
17. Tochigi N, Kishimoto T, Supraitna Y, Nagai Y, Nikaido T, Ishikura H. Hepatoid carcinoma of the ovary: a report of three cases admixed with a common surface epithelial carcinoma. *Int J Gynecol Pathol* 2003 Jul; 22(3): 266-71
 18. Hoshida Y, Nagakawa T, Mano S, Taguchi K, Aozasa K. Hepatoid adenocarcinoma of the endometrium associated with alpha-fetoprotein production. *Int J Gynecol Pathol* 1996 Jul; 15(3): 266 - 9
 19. Aoyama T, Mizano T, Andoh K, Takigi T, Mizumo T, Eimoto T. Alpha-fetoprotein-producing (hepatoid) carcinoma of the fallopian tube. *Gynecol Oncol* 1996 Nov; 63(2): 261 - 6
 20. Ishikura H, Kirimoto K, Shumoto M. Hepatoid adenocarcinoma of the stomach: An analysis of seven cases. *Cancer* 1986 Jul; 58(1): 119 - 26
 21. Nogales FF, Concha A, Plata C, Ruiz-Avila I. Granulosa cell tumor of the ovary with diffuse true hepatic differentiation simulating stromal luteinization. *Am J Surg Pathol* 1993 Jan; 17(1): 85 - 90
 22. Ulbright TM, Roth LM, Brodhecker CA. Yolk sac differentiation in germ cell tumor. A morphological study of 50 cases with emphasis on hepatic, enteric and parietal yolk sac features. *Am J Surg Pathol* 1986 Mar; 10(3): 151 - 64
 23. Young RH, Perez-Atayde AR, Scully RE. Ovarian Sertoli-Leydig cell tumor with retiform and heterologous components. Report of a case with hepatocytic differentiation and elevated serum alpha-fetoprotein. *Am J Surg Pathol* 1984 Sep; 8(9): 709 - 18
 24. Chadha S, Honnebier WJ, Schaberg A. Raised alpha-fetoprotein in Sertoli-Leydig cell tumor (androblastoma) of ovary: report of two cases. *Int J Gynecol Pathol* 1987; 6(1): 82 - 8
 25. Donaldson ES, Van Nagell Jr JR. Multiple biochemical markers in patients with gynecologic malignancies. *Cancer* 1980; 45: 948 - 53
 26. Otis CN, Powell JL, Barbuto D, Carcangiu ML. Intermediate filamentous proteins in adult Granulosa cell tumors. An immunohistochemical study of 25 cases. *Am J Surg Pathol* 1992 Oct; 16(10): 962 - 8
 27. Aguirre P, Thor AD, Scully RE. Ovarian endometrioid carcinomas resembling sex cord-stromal tumors tumor. An immunohistochemical study. *Int J Gynecol Pathol* 1989; 8(4): 367 - 73
 28. Aguirre P, Thor A, Scully RE. Ovarian small cell carcinoma. Histogenetic considerations based on immunohistochemical and other findings. *Am J Clin Pathol* 1989 Aug; 92(12): 140 - 9
 29. Benjamin E, Law S, Bobrow LG. Intermediate filaments cytokeratin and vimentin in ovarian sex cord- stromal tumours with correlative studies in adult and fetal ovaries. *J Pathol* 1987 Aug; 152(4): 253 - 63
 30. Pinkerton JH, McKay DG, Adams EC, Hertig AT. Development of the human ovary—a study using histochemical technic. *Obstet Gynecol* 1961 Aug; 18: 152 - 81
 31. Holthofer H, Miettinen A, Lehto VP, Lehtonen E,

Virtanen I. Expression of vimentin and cytokeratin types of intermediate filament preteins in developing and adult human kidneys. *Lab Invest* 1984 May; 50(5): 552 - 9

32. LaRocca PJ, Rheinwald JG. Coexpression of

simple epithelial keratins and vimentin by human mesothelium and mesothelioma in vivo and in culture. *Cancer Res* 1984 Jul; 44(7): 2991 - 9