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Report

Ovarian Sertoli-Leydig Cell Tumor with a Component Which Differentiated into Hepatocytes and Produces High Serum Alpha-Fetoprotein

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A 72-year-old patient presented with a stage I left ovarian Sertoli-Leydig cell tumor and raised serum alpha-fetoprotein levels. Less than 30 cases of Sertoli-Leydig cell tumor that produce alpha-fetoprotein have been reported in the English literature. In these reports, alpha-fetoprotein was expressed in the Leydig, Sertoli, hepatoid, undifferentiated and gastrointestinal cells. In our case, alpha-fetoprotein was positive in swollen and vacuolated cells containing glycogen granules. These cells have little histological resemblance to hepatocytes but were positive for hepatocyte specific antigen (OCH1E5). These findings show that alpha-fetoprotein producing cells can differentiate into hepatocytes.

This is the first case of ovarian Sertoli-Leydig cell tumor in which alpha-fetoprotein producing cells differentiated into hepatocytes, as identified by positivity for OCH1E5.

Key words: ovary, Sertoli-Leydig cell tumor, alpha-fetoprotein, hepatocyte, hepatocyte specific antigen (OCH1E5)

Introduction

Ovarian Sertoli-Leydig cell tumor (SLCT) is a rare disease, and it is even rarer to encounter a case with raised serum alpha-fetoprotein levels. To our knowledge, less than 30 cases of alpha-fetoprotein producing SLCT have been reported in the literature[1)~22)]. We report here a case of ovarian SLCT with high serum alpha-fetoprotein levels produced by cells which differentiated into hepatocytes.

Case Report

1. Clinical summary

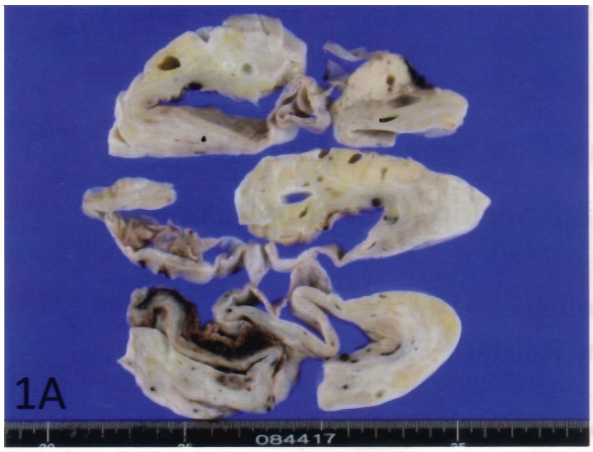
A 72-year-old woman complained of abnormal vaginal bleeding for 1 year and consulted our hospital about the abdominal pain and the vaginal bleeding. There was no past history of similar symptoms. She was 2-gravida 2-para. A transvaginal ultrasound revealed the presence of an intrapelvic multilocular mass. Preoperative levels of serum alpha-fetoprotein and cancer antigen 125 (CA125) were elevated to 862.9 ng/ml (<20) and 170 u/ml (<35) respectively. Serum concentrations of estradiol (71 pg/ml, normal value after menopause is<39), progesterone (0.39 ng/ml, postmenopausal norm is <0.2), and testosterone (0.39 ng/ml, normal value after menopause is <0.08) were elevated. Levels of follicle-stimulating hormone (FSH) (3.45 mIU/ml, normal range after menopause is 34.8-190.4) and luteinizing hormone (LH) (6.22 mIU/ml, normal range after menopause is 8.7-68.1) were low. A laparotomy disclosed a left ovarian mass, thus a total abdominal hysterectomy with bilateral salpingo-oophorectomy and partial omentectomy were performed.

2. Pathological findings

1) Macroscopic findings

The left ovary was 23 × 17 × 13 cm in size and weighed 3,700 g. Its surface was smooth, and on the sectioned surface, the tumor showed cystic and solid regions. The solid portion displayed yellow and white coloration with zonal hemorrhage, and contained white fleshy foci (Fig. 1).

The left fallopian tube and the right adnexa were normal. The uterus, measuring 9.5 × 5.5 × 4 cm in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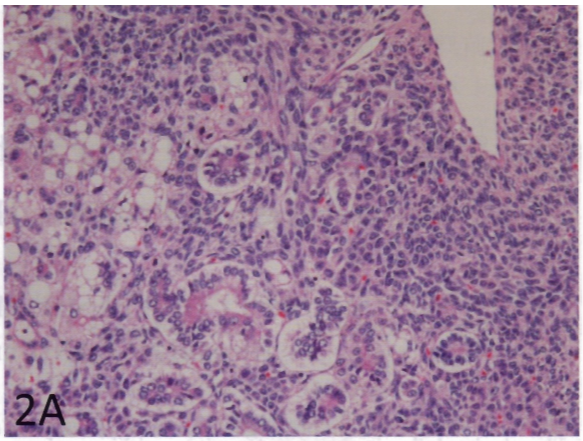
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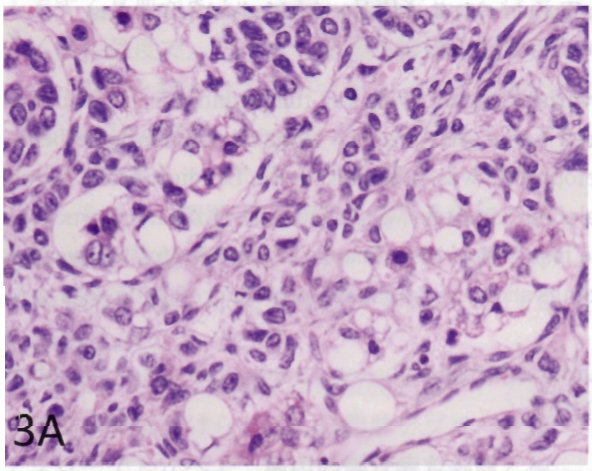
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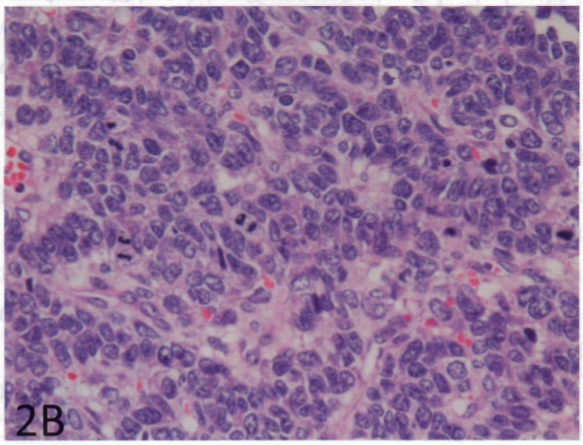
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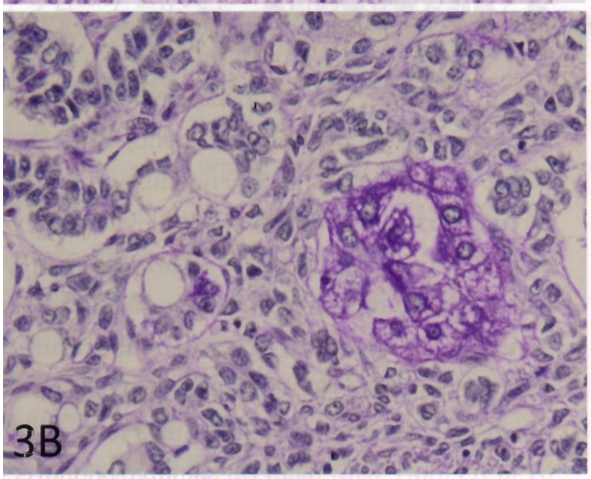
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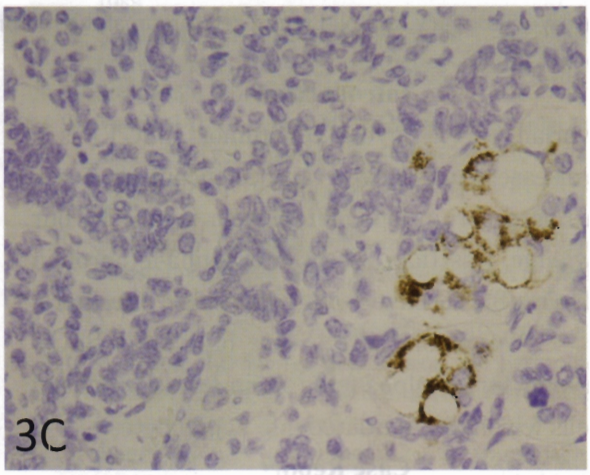
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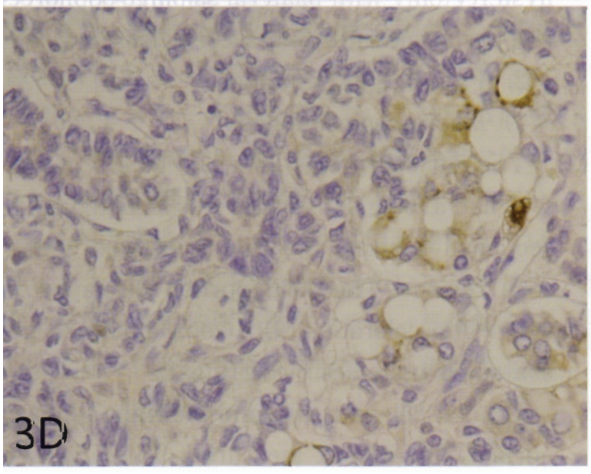
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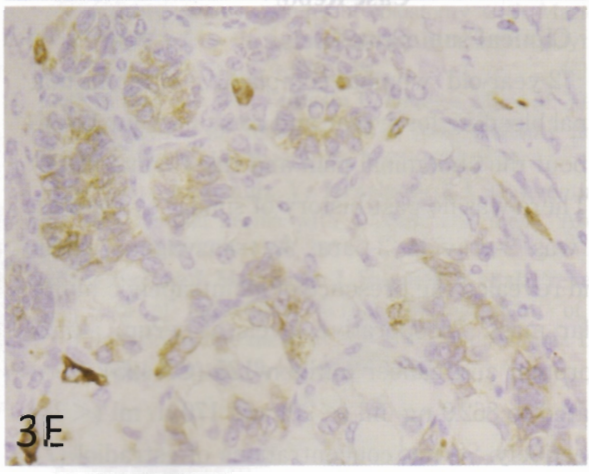
3E

size, had several leiomyomas up to 2.5 cm in diameter, and an endometrial polyp 15×5×3 mm in size. The omentum was not involved.

2) Microscopic findings

The epithelioid patterns were intermingled with a stromal component that varied from fibrous to cellular to edematous, and often separated by a fibrous stromal component. The Sertoli cells formed round or closed and occasionally confluent tubules. There was an area with microfollicle-like pattern. The appearance of the tubule-forming cells was variable, which showed either columnar to cuboidal cytoplasm with elongated nuclei or clear cytoplasm with nuclei localized at the base. These tubules were situated among short, irregularly-arranged spindle cells with high nuclear to cytoplasmic ratio. The Leydig cells, which were arranged in a diffuse pattern or in nests, were admixed with tubules and short spindle cells, and appeared either eosinophilic or swollen and vacuolated (Fig. 2A). In the white fleshy areas, the short spindle cells dominated, showing a highly cellular phenotype and had a high mitotic rate, as observed in maximum 20/10 high power field (Fig. 2B). Based on the World Health Organization criteria[23], this tumor was classified as intermediately differentiated SLCT because Sertoli cells formed predominantly closed tubules and showed densely cellular growth composed of immature Sertoli cells, and contained minor foci of poorly differentiation.

There was no retiform pattern nor heterologous element.

3) Immunohistochemical findings

Formalin-fixed and paraffin-embedded sections were deparaffinized and immunostained using serially sectioned slides for epithelial membrane antigen (EMA), cytokeratin (AE1/AE3), carcinoembryonic antigen (CEA), inhibin α, calretinin, CD56, chromogranin A, alpha-fetoprotein, hepatocyte specific antigen (OCH1E5), cytochrome P450scc (P450scc), estrogen receptor (ER), progesterone receptor (PgR) and MIB-1, using the Envision system (Dako, Glostrup, Denmark). Antigen retrieval was conducted for some antibodies by microwave treatment, in accordance with the manufacturer's protocol (Table 1).

Inhibin α was expressed in the tubule-forming cells, and in the swollen and vacuolated cells. Calretinin was expressed in the same cells that were positive for inhibin α as well as in the short spindle cells. EMA and CEA were not expressed in any of the detected cells. The tubule-forming cells and the cells resembling Leydig cells were both positive for CD56 and AE1/AE3. P450scc was expressed in the luteinized cells amidst short spindle cells. Several closed tubules were positive for chromogranin A. ER was expressed with moderate intensity in some of the tubules, whereas PgR was expressed in more than half of the short spindle cells with moderate intensity and intensely expressed in some of the tubules. The short, spindle cells with high mitotic rate showed a MIB-1 index of 40% while other areas showed 10-15%.

The swollen and vacuolated cells, which contained glycogen granules identified by periodic acid-Schiff (PAS) staining, expressed alpha-fetoprotein and inhibin α were also positive for OCH1E5 in the same tumor nest (Fig. 3).

Fig. 1 Gross image of the resected ovary
On the sectioned surface, we observed yellowish solid regions and cystic spaces with zonal hemorrhage, and a white fleshy portion at the upper right.

Fig. 2
A. Hematoxylin-eosin, original magnification ×200
Sertoli-cells arranged in discrete, round tubules and clusters of vacuolated or eosinophilic cells resembling Leydig-cells amidst short, spindle cells.
B. Hematoxylin-eosin, original magnification ×400
Short, irregularly arranged spindle cells with high nuclear to cytoplasmic ratio and high mitotic rate.

Fig. 3 Vacuolated and swollen cells in clusters of the same tumor nest are immunopositive for OCH1E5, alpha-fetoprotein and inhibin α
A. Hematoxylin-eosin stain, original magnification ×400.
B. The same cells from Fig. 3A contain glycogen granules. Periodic acid-Schiff stain, original magnification ×400.
C. OCH1E5 is immunopositive in the same cells, original magnification ×400.
D. The same cells are also alpha-fetoprotein-positive, original magnification ×400.
E. Inhibin α is expressed in the same cells, original magnification ×400.

Table 1 Antibody used in the study

Antibody	Clone	Dilution	Source	Antigen Retrieval
EMA	E29	1 : 400	Dako	(−)
AE1/AE3	AE1/AE3	1 : 200	Dako	Microwave
CEA	CEM010	1 : 200	TaKaRa	(−)
Inhibin α	R1	1 : 50	Dako	Microwave
Calretinin	SP13	Diluted	Zymed	Microwave
CD56	1B6	1 : 50	Novocastra	Microwave
Chromogranin A	DAK-A3	1 : 750	Dako	(−)
Alpha-fetoprotein	polyclonal	1 : 200	Dako	(−)
Hepatocyte	OCH1E5	1 : 750	Dako	Microwave
P450scc	polyclonal	1 : 800	CHEMICON	(−)
ER	1D5	1 : 50	Dako	Microwave
PgR	PgR636	1 : 800	Novocastra	Microwave
Ki-67 (MIB-1)	MIB-1	1 : 100	Dako	Microwave

Table 2 Alpha-fetoprotein-positive cells in reported cases

Case	Age (year)	α-fetoprotein (serum)	Degree of differentiation	AFP-positive cells
1[1]	16	over 400 ng/ml	Poor	ND
2[2]	ND	158 ng/ml	ND	ND
3[3]	13	14,000 ng/ml	Poor	Hepatoid cell
4[4]	16	40 IU/ml	Int	L-cell, S-cell
5[5][6]	0.9	7,000 ng/ml	Int	L-cell, S-cell
6[7]	21	109 ng/ml	Int	Unidentified cell
7[8]	16	62 IU/ml	ND	ND
8[9]	27	138,400 ng/ml	Poor	L-cell, Luteinized cell
9[10]	17	256 ng/ml	Poor	L-cell
10[11]	25	2,600 ng/ml	Int	L-cell
11[12]	16	4,500 ng/ml	Int	S-cell
12[12]	11	1,500 ng/ml	Int	Hepatoid cell
13[13]	12	380 ng/ml	Int	L-cell, S-cell
14[14]	18	1,443 ng/ml	Int	S-cell
15[15]	17	256 ng/ml	ND	L-cell
16[16]	15	200 ng/ml	Int	NT
17[17]	17	194 ng/ml	Int	Hepatoid cell
18[18]	24	850 ng/ml	Int ~ Poor	ND
19[19]	17	40 ng/ml	Int	L-cell
20[20]	27	213 ng/ml	Int	Endometrioid-like tubule
21[21]	44	ND	Poor	Hepatocyte
22[21]	74	ND	Int	Hepatocyte
23[21]	18	ND	Poor	Hepatocyte
24[21]	23	ND	Int	Hepatocyte
25[21]	15	ND	Poor	Hepatocyte
26[22]	20	306 ng/ml	Poor	Gastrointestinal cell
27*	72	863 ng/ml	Int>Por	☆

ND: not described, Int: intermediate, NT: not tested, L-cell: Leydig cell, S-cell: Sertoli cell.
*: our case, ☆ : cells with a hepatocyte immunophenotype.

Discussion

In SLCT, alpha-fetoprotein is expressed in the Leydig, Sertoli, hepatoid, and gastrointestinal cells, as reported in the literature[1)~22)] (Table 2). The Leydig cells are essentially in the stroma of the testis, show eosinophilic or clear cytoplasm, and frequently contain lipids[24)25)]. In Sertoli-Leydig cell tumors, Leydig cells that are of ovarian sex cord-stromal derivation, show variable degrees of maturation, therefore, as shown in previous reports[1)~22)], Leydig cells with immunopositive for alpha-fetoprotein exhibit variable degrees of immaturity.

In our case, although the alpha-fetoprotein-positive cells showing swollen and vacuolated had histological resemblance to immature Leydig cells rather than hepatocytes, the immunohistochemical findings showed that these cells were positive for OCH1E5, which is indicative of differentiation into hepatocytes. Wennenberg et al. originally presented the development of a new monoclonal antibody Hepatocyte Specific Antigen Hep Par 1 (OCH1E5), which is a monoclonal antibody that reacts specifically with normal adult, fetal, and neoplastic hepatocytes[26]. Its staining pattern is very distinct, showing granular and cytoplasmic localization. They speculated that the antigen may be mitochondria-associated in a tissue-dependent manner, since the antigen was not expressed in mitochondria-rich kidney tubules and skeletal muscle. In our case, the findings that these cells showed cytoplasmic immunoreactivity for OCH1E5, but contained no bile pigments and formed no bile plugs, imply that these cells displayed an immature hepatocyte phenotype. These cells also had immunohistochemical characteristics of the sex cord-stromal cells.

Many neoplastic conditions of the ovary contain either organized hepatic tissue or less-organized hepatocyte clusters. In sex cord-stromal tumors, adult-type granulosa cell tumors have foci of hepatocytes[27]. Further, germ cell tumors, yolk sac tumors[28] and immature teratoma[29] also show focal hepatoid features. Even surface epithelial tumors such as endometrioid carcinoma express hepatoid differentiation[30]. In these tumors, the hepatic tissue or the hepatoid cells demonstrate positivity for alpha-fetoprotein. Alpha-fetoprotein is physiologically produced in the yolk sac and the fetal liver, and has been used as a serum marker for the diagnosis of yolk-sac tumor and hepatocellular carcinoma. Yet, it is detected in various ovarian germ cell tumors other than yolk sac tumors as well as non-germ cell tumors such as SLCT[3]. Alpha-fetoprotein has been detected not only in cells with hepatocyte features, but also in the primitive mucin-secreting gastrointestinal epithelium of SLCT[21]. The mechanism of alpha-fetoprotein production in SLCT is unknown, but the fact that SLCT lacks elements of germ cell tumors, as in our case, indicates that alpha-fetoprotein producing cells are derived from somatic cells by transdifferentiation or dedifferentiation. In addition, the finding that hepatoid adenocarcinomas, which occur in various organs including stomach[31], colon[32] and pancreas[33], hold lectin affinities associated with each organ[34][35] supports our hypothesis.

To the best of our knowledge, this is the first case of ovarian SLCT in which components displayed differentiation to an alpha-fetoprotein producing hepatocyte phenotype, as proven by immunopositivity for OCH1E5.

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腫瘍内に肝細胞への分化を示す成分を含み，血中 AFP が高値であった卵巣セルトリ・ライディク細胞腫の１例

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Alpha-fetoprotein（AFP）を産生する卵巣のセルトリ・ライディク細胞腫は非常にまれで，英文の報告例は 30 に満たない．72 歳の左卵巣に発生した臨床 I 病期のセルトリ・ライディク細胞腫で AFP が高値を示した症例を報告する．

AFP 陽性細胞の多くは胞体が腫大，あるいは空胞状を示し，グリコーゲン顆粒を含んでおり，さらに免疫染色で Hepatocyte Specific Antigen（OCH1E5）陽性の所見を得た．

これまでの報告例では AFP 陽性細胞は組織学的にライディク細胞，セルトリ細胞，肝細胞類似の細胞，未分化な細胞，そして消化管上皮細胞に見出されている．本症例の AFP 陽性細胞は組織学的には肝細胞に似ていなかったが，胎児・成人の正常肝および腫瘍性肝細胞に特異的に反応する OCH1E5 が陽性であることから，肝細胞への分化を示すことが明らかとなった．

卵巣のセルトリ・ライディク細胞腫で，AFP 陽性細胞の肝細胞への分化が OCH1E5 陽性の所見によって確認された最初の報告例である．