

## Clear Cell Carcinoma of the Ovary

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Clear cell carcinoma is not a common tumor: it comprised only 4.1 per cent of all ovarian cancers in Korea (Ahn, 1982). This tumor has been variously termed mesonephroid tumor, mesonephroid carcinoma, mesonephroma, mesonephric carcinoma, adenocarcinoma of mesonephric type, mesometanephric rest tumor, mesometanephroma, parvilocular cystoma, Grawitz tumor of ovary, and hypernephroid carcinoma. Schiller (1939) is the first to delineate the distinct histopathologic findings of "mesonephroma". He described ten cases of female genital tract tumors consisting of tubular or cystic papillary structure associated with "hobnail cells" and glomerulus-like bodies. Later Teilum (1954 & 1959) maintained that Schiller's group of tumors was heterogeneous and comprised two sub-groups, endodermal sinus tumor and the "Mesonephric" (now called as clear cell) neoplasms. Teilum (1959) demonstrated that there were great similarities between glomerulus-like structure and endodermal sinus of rodent.

In 1967 Scully and Barlow (1967) analyzed 28 cases of "mesonephroma" and found high incidence of pelvic endometriosis, frequent admixtures of endometrioid carcinoma, and 7 cases in which the tumors arose from the epithelium of endometriotic cyst. They believed that the "mesonephroma" is müllerian in origin and that the former is closely related to endometrioid carcinoma.

The fact that foci of endometriosis could not be demonstrated in many cases of "mesonephroma" prompted second theory of origin: pleuripotential ovarian surface epithelium was sug-

gested as origin (Norris and Robinowitz, 1971; Kurman and Craig, 1972; Fine et al., 1973). The third theory propose pleuripotential mesothelium as an origin, that was suggested by Rogers and colleagues (1972).

Despite these controversies clear cell carcinoma of the ovary is considered to be distinct clinico-pathologic entity.

On retrospective review of Korean literature (Cho et al., 1974; Park et al., 1975) and surgical pathology files in Department of Pathology, College of Medicine, Seoul National University there appears to be some confusion in the usage of the term "mesonephroma" or clear cell carcinoma.

In this communication the author intends to summarize the clinico-pathologic findings of clear cell carcinoma compiled from surgical pathology files, Department of Pathology, Seoul National University Hospital, from 1968 to 1981. Furthermore, some search will be made on the histogenesis of this controversial tumor.

### MATERIAL AND METHOD

A review of 726 ovarian tumor removed at the Seoul National University Hospital from 1968 to 1980 yielded 5 tumors composed mainly of clear cells. In 1981 we encountered another tumor composed of clear cells. These 6 clear cell tumors comprised the base of this study. Clinical and pathologic features were studied in detail. Hematoxylin-eosin, mucicarmine, PAS, and d-PAS stains were done. In collecting the specimen we selected only those tumors which

satisfy the definition of clear cell carcinoma established by Scully (1979): tumors characterized by clear epithelial cells containing abundant cytoplasmic glycogen and hobnail (peg-shaped) cells, either alone or in combination.

Detailed microscopic examination was made to determine whether there is any association with malignant tumor other than clear cell carcinoma, any evidence of origin of the tumor from endometriosis, or any association with endometriosis. Detailed review on clinical history was done to find out any specific history in this peculiar tumor.

## RESULTS

**Incidence:** Five cases of clear cell carcinoma (4.1%), previously diagnosed as clear cell carcinoma, mesonephroid carcinoma, or serous cystadenocarcinoma, were uncovered. Another case was incidentally uncovered in 1981.

**Clinical features:** The clinical features were

tabulated in table 1.

**Age:** The mean age was 58 years, with a range from 46 to 75 years.

**Presenting symptoms:** The patients usually presented lower abdominal pain(4 cases), palpable abdominal mass(4 cases), and lower abdominal distention(2 cases).

**Duration of symptoms:** In 4 out of 6 cases the presenting symptoms developed 4 months prior to admission. In the other 2 patients the durations of symptoms were 1 year and 20 years.

**Parity:** Of the 3 cases on which record of parity was available, two patients were nulliparous; in the other patient the parity was 2-0-0-2.

**Treatment:** Four patients underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy, one total abdominal hysterectomy and unilateral salpingo-oophorectomy, and one unilateral salpingo-oophorectomy alone. Four patients received chemotherapy in addition and one patient received radiation therapy in

**Table 1.** Clinical and pathologic features of the clear cell carcinoma\*

Case No.	Age.	Side	Max. diam. ovary (cm)	Assoc. endometriosis	Presenting symptom	Tumor, gross appearance	Stage	Grade	Therapy	Follow-up
1. S72~892	55	R	16.5	—	Palpable mass & lower abd. pain, 3mo.	Partly cystic partly solid gray yellow	II a	II	U-0-0-S-S Radiotherapy	L-W 2yr.
2. S76~1306	46	L	18	—	Lower abd. pain & abd. mass, 1yr.	Partly cystic partly solid	III	II-III	U-0-0-S-S Chemotherapy	Live with carcinoma 1yr.
3. S77~5274	55	R	13	—	Palpable mass & lower abd. pain, 2mo.	Partly cystic partly solid gray yellow	I a	II	U-0-S	Lost to follow-up
4. S79~4889	57	L	18	—	Lower abd. distension, 4mo	Partly cystic partly solid yellow red	I a	III	U-0-0-S-S Chemotherapy	L-W 2y-4mo.
5. S79~7902	56	R	9	—	Abd. pain & abd. distension, 3 mo.	Solid hemorrhagic	III	II-III	0-S Chemotherapy	Live with cancer 3mo.
6. S81~13504	63	R	14	+ salpinx	Lower abd. mass, 20yr.	Partly cystic partly solid gray yellow	II a	III	U-0-0-S-S Chemotherapy (melphalan)	Live, 1mo.

\* Abbreviations U: Hysterectomy; O: Oophorectomy; S: Salpingectomy; L-W: Live and well.

Table 2. Histopathologic findings of clear cell carcinoma\*

Case No.	Clear cell	Hobnail cells	Papillary structure	Parvilocular cystoma-like	Associated Ovarian carcinoma	Origination from endometriotic cyst
1	+	##	+	—	—	—
2	##	###	##	##(50%)	—	—
3	###	—	—	—	—	—
4	##	+	##	—	—	—
5	##	—	—	—	endometrioid carcinoma	—
6	##	+	+	—	endometrioid carcinoma	+

\* +: Focal

##: More than focal

###: Total or abundant

addition.

**Survival:** The follow-up period was short in all patients. One case was lost to follow-up. Five cases, on whom follow-up information was available were alive; two with residual/or recurrent carcinoma. The follow-up period ranged from 1 month to 2 years and 4 months.

#### Pathologic features

**Gross:** All 6 cases involved only one side of the tumor.

Four cases involved right ovary; two involved left ovary. The tumors varied in size from 9 to 18cm, the mean diameter of the tumor was 14.8cm. Five tumors were partly cystic and partly solid gray yellow tumors; one two was solid hemorrhagic.

**Microscopic:** The microscopic findings are as tabulated in table 2. The striking features of this tumor was the presence of clear cells. The clear cells were polyhedral with distinct cell membranes and abundant clear cytoplasm. The nuclei were eccentric. The cytoplasm was rich in glycogen, which was demonstrable by PAS positive and d-PAS negative reaction of glycogen. The clear cells formed tubules, solid band or broad sheets. In areas the tumor cells have dark eosinophilic granular cytoplasm as seen in dark cell of renal cell carcinoma. Hobnail cells were encountered in 4 cases. The hobnail cells were characterized by prominent bulbous nuclei

protruding into cystic spaces beyond the limit of the cytoplasmic margin of the individual cell. In some of the extremely dilated cystic structure the tumor cells were markedly flattened. The cystic or tubular spaces contain acidophilic secretion, which was mucicarmine positive; the tumor cells were mucicarmine negative. In one case (case 4) an acidophilic round substance was noted in the center of the tumor cells, presenting a targetoid appearance. Papillary growth of the tumor was noted in four cases; the former consisting of fibrous tissue core with clear cell lining, which showed some resemblance to Schiller-Duval body but is somewhat different from classic Schiller-Duval body.

In one case (case 2) there were cystic structures with flattened simple clear cells or hobnail cells in the background of abundant fibrous stroma, simulating parvilocular cystoma described by Schiller (1942). Hyaline condensation of basement membrane material was noted, especially in the cores of papillae. Necrosis of tumor tissue was noted in all 6 cases, most prominent in cases 5 and 6.

Mitotic figures and moderate cellular pleomorphism were noted in all the cases. The histologic gradings were grade II in 2 cases, grade II-III in 2 cases, and grade III in 2 cases. Endometriosis was noted in the salpinx of case 6. In this case the tumor arose from the epit-

helium of the endometriotic cyst. In case 3 the tumor arose from unilocular cystic mass, but transition from endometriosis to clear cell carcinoma could not be demonstrated microscopically. In cases 5 and 6 the tumor contained foci of endometrioid carcinoma, but the latter comprised only a small portion of the tumor.

## DISCUSSION

The presence of focus of endometriosis with transition to overt carcinoma and association with endometriosis in salpinx indicate müllerian origin of this tumor, as suggested by Scully and Barlow (1967). The coexistence of typical endometrioid carcinoma in the same tumor also support müllerian origin of this tumor and that this tumor is related to endometrioid carcinoma.

But the absence of associated endometriosis in cases 1-5 suggests origin from pluripotential ovarian surface epithelium (Norris and Robinowitz, 1971). Kurman and Craig (1972) and Fine, et al. (1973) also supported origin from pluripotential ovarian surface epithelium and considered displaced endometrium as a less common source of origin. Their theoretical background was as follow: 1) mixed histologic pattern; 2) association with endometriosis, endometrioid carcinoma, and malignant transformation of the surface-covering cells of the ovary.

The discrepancy between the müllerian origin by Scully and Barlow (1967) and surface epithelial origin by Kurman and Craig (1972), Norris and Robinowitz (1971), and Fine and Clarke (1973) may originate from differences in incidence of associated endometriosis: in Scully's series (1967) of 11 selected cases, "seven arose as single or multiple papillary or polypoid masses from the lining of a large endometrial cyst"; in the latters the association of endometriosis was absent (Norris and Robinowitz, 1971) or

very low (Kurman and Craig, 1972).

Another interesting view, indicating an origin from pluripotential mesothelium, was suggested by Rogers, et al (1972). This view of mesothelial origin was supported by electron microscopic study of Okagaki and Richart (1970) indicating similarity between the ovarian tumor cells and the mesothelial cell. Woodruff (1979) extended this view and stated as follows: "The mesothelium overlying the embryonic gonad is the same as that which invaginated into an adjacent area to form the paramesonephric duct. From this duct arise all of the epithelial lining of the upper genital canal, namely, the mucinous variety of the endocervical canal. The endometrioid of the uterine cavity and the endosalpingeal or tubal types leave by invagination of this mesothelium into the ovary during later life. If the appropriate stimulus is present, the mesothelium may be converted into one of these three classic cell types."

But considering the classical histologic pattern of mesothelioma and clinical course which are different from ovarian tumors in general, it does not seem to be reasonable to categorize the well established ovarian tumors into the single entity "mesothelioma". After all all three suggested tissue of origin derives from coelomic epithelium. In the first two theories, müllerian and ovarian surface epithelial origin, a potential for müllerian differentiation is developed in the tissue of müllerian origin, and latent until stimulated in the tissue of ovarian surface epithelial origin, while in the third theory tissue of origin appears to have progressed sufficiently far along the developmental cell line that it has lost capacity for such differentiation as suggested by Eastwood (1978). Mesonephric origin originally suggested by Schiller (1939), and later supported by Wade-Evans and Langley (1961), and Novak, et al. (1954, 1959), can be excluded on the ground that tubular pattern of growth and clear cells

have no specific meaning in regard to the origin or nature of a tumor and majority of cases occur along the course of müllerian duct as well as within the ovary where no mesonephric remnants are found.

In summary the tumor seems to originate from surface epithelium of ovary but in rare cases such as in case 6, the tumor can originate from endometriosis.

The incidence of clear cell carcinoma is similar to those of Kurman and Craig (5%, 1972), but lower than that of Czernobilsky, et al (10.7%, 1970). The mean age of 58 years is a little bit older than those of Czernobilsky, et al (53.2 years, 1970), Kurman and Craig (54 years, 1972), and Norris and Robinowitz (48 years, 1971). The presenting symptoms are similar to those of Czernobilsky, et al (1970) and Norris and Robinowitz (1971). The Czernobilsky's series (1970) contained relatively high proportion of nulliparous women as indicated in the present series.

The number in the present series was too small and follow-up period was very short to give any information that any therapy was of greater benefit than other mode of therapy. But patients with solid form of tumor and in advanced clinical stage seem to have worse prognosis.

The clear cell carcinoma should be distinguished from endodermal sinus tumor, endometrioid carcinoma, dysgerminoma, papillary serous cystadenocarcinoma, lipid cell tumor. Typical perivascular formations and microcystic structure, age of the patient (children and young adult vs old lady) and secretion of  $\alpha$ -fetoprotein will be useful guides in the diagnosis of endodermal sinus tumor. In endometrioid carcinoma the tumor has identical structure as seen in endometrial adenocarcinoma; short glandular pattern is prominent. Clear cells and tubules may be seen in endometrioid carcinoma but classic cystic structure with hobnail cells and the

variation in pattern from one part of the neoplasm to another in clear cell carcinoma are absent in endometrioid carcinoma. Clear cells may be present in mucinous and serous cystadenocarcinoma, but typical appearance of peg-like cells in serous carcinoma and mucinous epithelium permits their identification. The adenomatoid tumor is usually small and small cystic spaces are lined by loose or dense fibrous tissue in which smooth muscle is frequently noted. The cystic spaces seem to be a confluence of vacuolation of individual epithelial-like cells. Presence of hob-nail cells, absence of lymphocytes and granulomas and typical eccentrically located nuclei and old age of the patient will be helpful in excluding the possibility of dysgerminoma. Clinical finding and fat stain usually establish the diagnosis of lipid cell tumor. Metastatic renal cell carcinoma may pose problem in differential diagnosis, but clinical data and roentgenologic study are helpful in excluding metastatic renal cell carcinoma.

### Summary

One hundred and twenty one cases of ovarian malignancy were reviewed over a period of 13 years from 1968 to 1980. Of these, 5 cases (4.1%) were classified as clear cell carcinoma. In 1981 one additional case of clear cell carcinoma was uncovered. The mean age of the 6 patients was 58 years, with a range from 46 to 75 years. Presenting symptoms were abdominal pain or mass and/or distention. One case was associated with salpingeal endometriosis and ovarian endometriosis with transition to clear cell carcinoma. The striking features were clear cells (6 cases) and hobnail cells (4 cases), but papillary structure (4 cases) and parvilocular cystoma-like area (1 case) were also noted. Patients with solid tumor and in advanced stage seemed to have a worse prognosis than those with partly

cystic and partly solid tumor and in less advanced stage.

Histogenesis of clear cell carcinoma was studied and discussed in detail: origin from the ovarian surface epithelium seems to be the most frequent tissue of origin but rarely the tumor originate from epithelium of endometriotic cyst.

＝圖文抄錄＝

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안 금 환

1968년부터 1980년까지 121례의 난소 악성종양을 재검색한 바 5례(4.1%)의 투명세포암이 관찰되었으며 1981년 1례의 난소 투명세포암이 관찰되어 도합 6례를 임상·병리학적으로 면밀히 검토한 바 다음과 같은 결과를 얻었다.

1. 투명세포암은 난소악성종양의 4.1%를 차지하였으며 환자의 평균연령은 58세였다.
2. 전 6례에서 종양은 한쪽 난소만 침범하였으며, 4례는 우측, 2례는 좌측 난소에서 발생하였다.
3. 환자의 주소는 하복부 동통(4례), 종괴촉지(4례) 및 하복부 팽만(2례)이었다.
5. 기록검토가 가능한 3례중 2례는 출산력이 없었다(nulliparous).
6. 육안적으로 5례는 충실성 및 남성구조가 혼재하고 1례는 충실성 조직으로 구성되었다. 현미경적으로 투명세포(6례), 및 "Hob-nail cell" (4례)가 나타나는 점이 특징이었으며 유두상 증식(4례), 및 Parvilocular cystoma와 유사한 부위(1례)도 있었다. 수반된 자궁내막증은 1례에서 수반관에 있었으며 동시에 난소의 자궁내막성 낭상피에서 투명세포암으로 이행하는 부위가 있었다. 전 6례중 2례에서는 자궁내막양 암(endometrioid carcinoma) 성분이 혼재되어 있었으나 그 양은 비교적 적었다.
7. 충실성 종양 및 진행된 암을 가진 환자의 예후는 충실성 및 남성조직이 혼재된 종양 및 덜 진행된 암을 가진 환자보다 예후가 불량한 경향을 보였다.
8. 종양세포의 기원은 난소표피상피(ovarian surface epithelium)의 가능성이 가장크며 드물게는 자궁내막중에서도 기원하리라 추정되었다.

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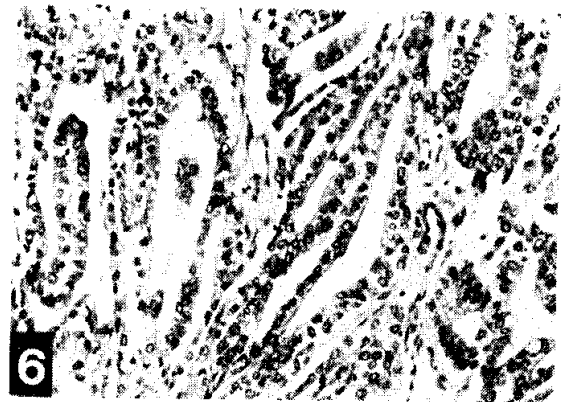
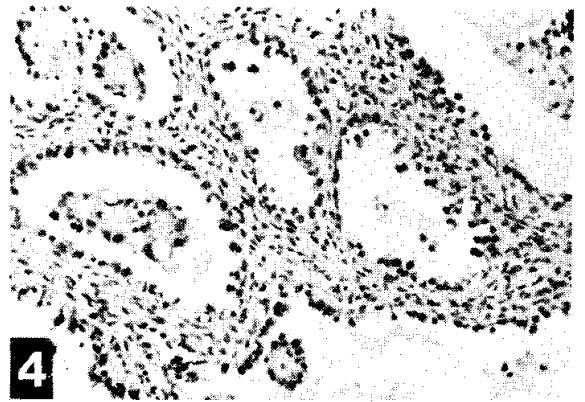
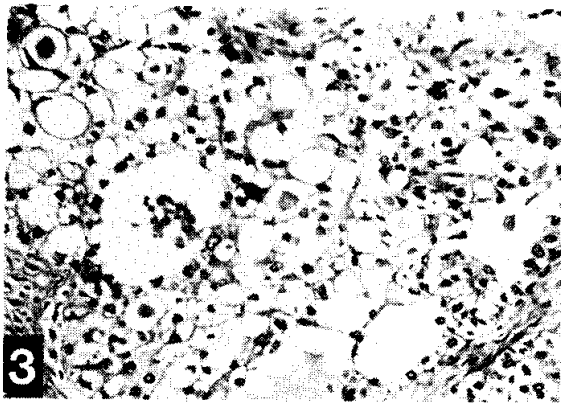
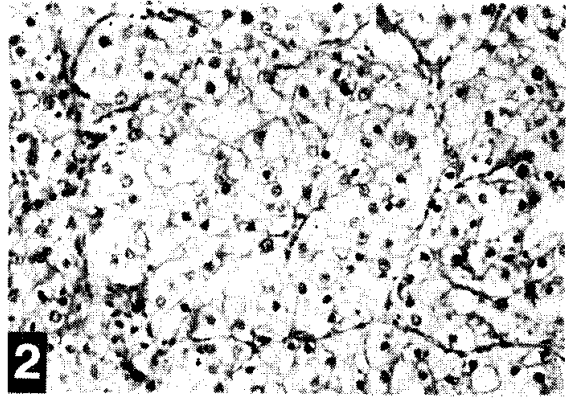
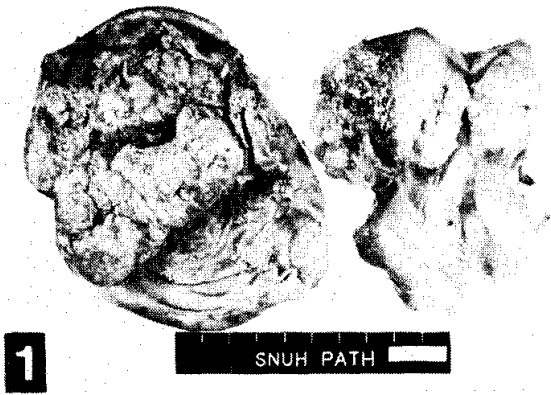
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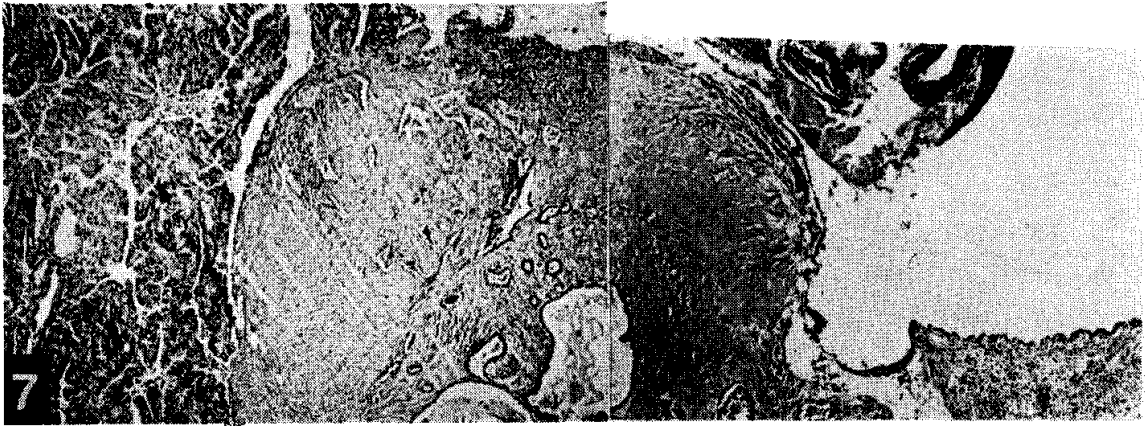
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**Fig.1.** Gross appearance of the tumor. Note solid nodular tumor mass protruding into the unilocular cystic space.

**Fig.2.** High power view of tumor, showing large polyhedral cells with clear cytoplasm. H. & E.  $\times 200$ .

**Fig.3.** High power view of clear cell carcinoma. Note intracellular accumulation of eosinophilic material presenting a targetoid appearance. H. & E.  $\times 200$ .

**Fig.4.** Parvilocular cystoma-like area, showing prominent hob-nail cells. H. & E.  $\times 200$ .

**Fig.5.** Papillary formation with hyalinization of fibrous core in clear cell carcinoma. H. & E.  $\times 200$ .

**Fig.6.** High power view of clear cell carcinoma, showing endometrioid carcinoma component. H. & E.  $\times 200$ .

**Fig.7.** Low power view of case 6, showing endometriosis (right hand side) transforming into clear cell carcinoma. H. & E.  $\times 100$ .