

# Juvenile Granulosa Cell Tumor of the Ovary

—Report of a Case of Malignant Form with Unusual Pleomorphism—

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## ABSTRACT

A case of Juvenile Granulosa Cell Tumor (JGCT) of the ovary with unusual pleomorphic histology and malignant biologic behaviour is described. The tumor occurred in a 10-year-old girl and was associated with clinical features of isosexual pseudoprecocity and a marked elevation of serum estradiol.

The mass manifested initially in the right ovary and subsequently involved the contralateral ovary. A multi-organ metastasis developed during a 6-month-interval despite chemotherapy. She received two operations at 6-month interval, and tissues were obtained from the tumor mass. A marked histologic difference was observed between these two samples. The second biopsy showed profound cellular pleomorphism with numerous multinucleated tumor giant cell formation and hyaline bodies. The differential diagnosis from germ cell tumor and the possible factors for the pleomorphism are discussed.

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**Key Words:** Juvenile granulosa cell tumor, Pleomorphism, Chemotherapy, Malignant ovarian tumor

## INTRODUCTION

The granulosa cell tumor of the ovary comprises less than 10 percent of all ovarian malignancies and among them, less than 5 percent of the cases encountered are in the prepubertal period<sup>1)</sup>. Scully<sup>2,3)</sup> described distinctive histologic features of these granulosa cell tumors occurring predominantly in the young age group and adopted the term juvenile granulosa cell tumor (JGCT) in contrast to the conventional granulosa cell tumor of adulthood.

The two basic microscopic growth patterns found

in JGCT are the diffuse solid or the macrofollicular pattern. Though a high degree of nuclear atypism was observed in some cases, marked pleomorphism with frequent giant cell formation has not been described among the histologic features of JGCT<sup>4,5)</sup>.

In this study, authors describe a case of JGCT with unusual pleomorphism and aggressive clinical behaviour, and possible factors responsible for the pleomorphism are discussed.

## REPORT OF A CASE

### Clinical summary

A 10-year-old girl was transferred to Seoul National University Children's Hospital (SNUCH) in November, 1988. She had been relatively healthy until September, 1988, when she incidentally noted

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an abdominal mass. The mass insidiously increased in size, and she visited a general hospital under the impression of ovarian tumor. The biopsy was interpreted as an endodermal sinus tumor, and she was transferred for further treatment.

During the period from November, 1988, to March, 1989, she received 6 cycles of anticancer chemotherapy with VPB (Vinblastin-Bleomycin-Cisplatin) regimen. Since March 22, 1989, she has complained of progressive abdominal distension, nausea and vomiting, and she visited SNUCH Pediatric Department. She was chronically ill-looking and tachypneic. Physical examination revealed features of isosexual precocious puberty such as breast enlargement and growth of pubic hair. An abdominal CT revealed a huge peritoneal mass, a solitary liver metastasis, multiple lymph node metastasis, and massive ascites.

The laboratory findings were as follows: CBC: Hgb 13.4 gm/dl; WBC: 16,900/mm<sup>3</sup> platelet 770,000/mm<sup>3</sup> BUN/Creatinine: 10 mg/dl/0.6 mg/dl, serum estradiol: 1,650 pg/ml (normal range;30~120pg/ml), protein/albumin: 5.2 gm%/2.7 gm%, alpha fetoprotein: 15 ng/ml (<20 ng/ml), HCG: 3 mlu/ml (<3 mlu/ml). FSH and LH levels were also within normal range.

On operation, a left ovarian mass involving the posterior wall of the uterus and omental dissemination was noted. A large amount of bloody ascites was also present. A left oophorectomy and partial omentectomy were done. Following the operation, the serum estradiol level decreased to 155 pg/ml, and the patient is now receiving chemotherapy with VAB-6 (Vinblastin-Cyclophosphamide-Actinomycin D-Bleomycin-Cisplatin) regimen.

### Pathologic findings

**Gross findings:** The left ovary was replaced by a huge mass, measuring 12×11×8 cm and weighing 440 gm. The mass was relatively well-circumscribed, and the external surface showed punctate hemorrhage. The cut surface was partly solid and partly



**Fig. 1.** The cut surface of a left ovarian mass. Entire tumor is deeply hemorrhagic and necrosis is profound. The variable cystic portions contained bloody serosanguineous fluid.

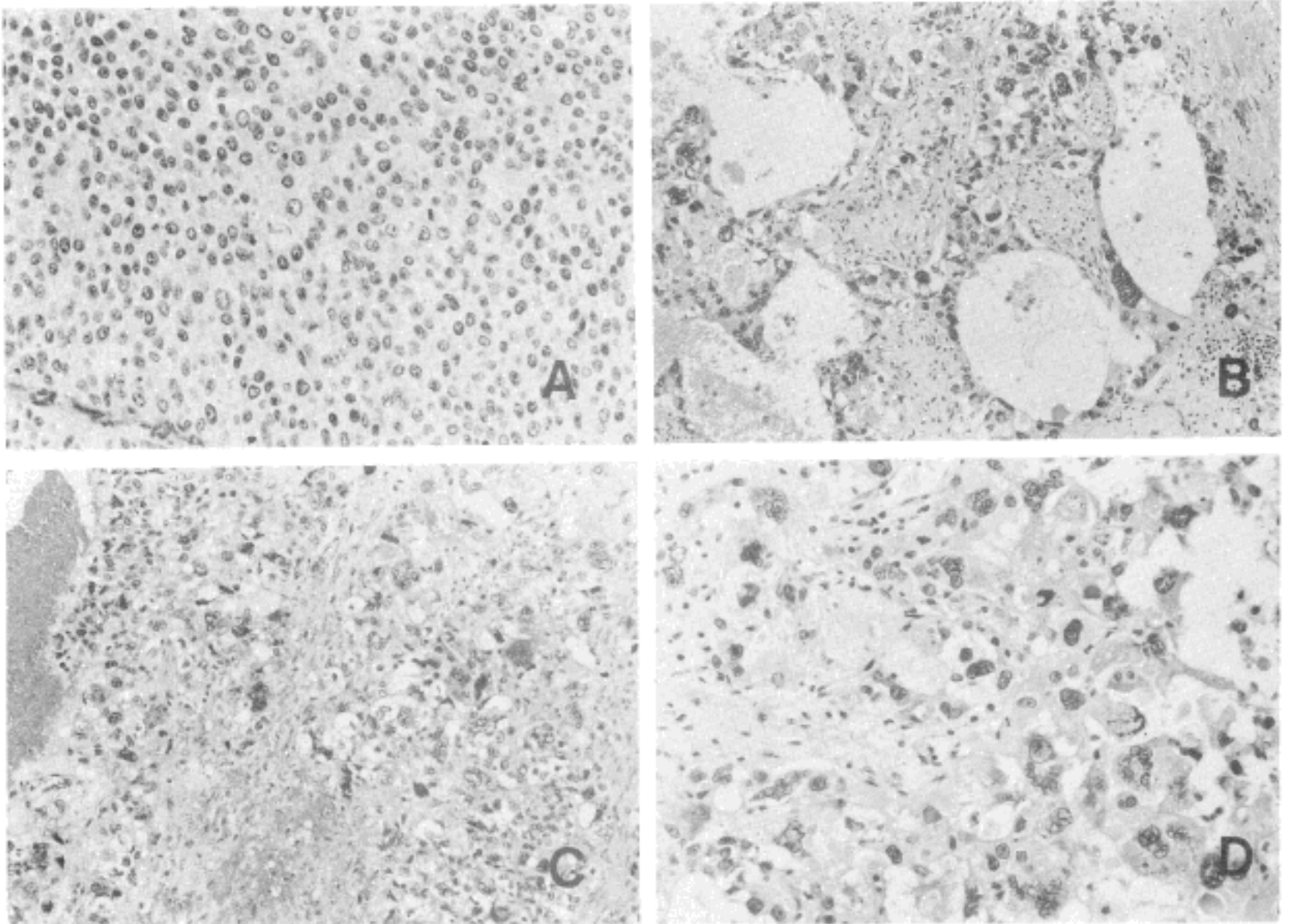
cystic. The necrotic areas were dusky yellow to tan and geographic in distribution (Fig. 1).

The cystic portions were filled with varying amount of dark red serosanguineous fluid and blood. The largest cystic portion measured 3.5 cm in maximal dimension. Fragments of submitted omentum showed multiple hemorrhagic tumor metastasis.

**Light microscopic and immunohistochemical findings:** Review of initial biopsy at another hospital showed a predominantly diffuse solid pattern of growth (Fig. 2a). There were also areas of follicular arrangement with individual cell luteinization. Fibrous stroma intervened nodular tumor cell nests. Cellular pleomorphism or giant cell formation was absent.

The second biopsy at SNUCH showed extensive tumor necrosis and an irregular macrofollicular arrangement of tumor cells (Fig. 2b). The nuclei were hyperchromatic, and a nuclear groove was not identified. The nuclei showed varying degrees of anaplasia, and multinucleated tumor giant cells simulating syncytiotrophoblast were frequently observed (Fig. 2c).

The mitotic count was unusually high, 50/10HPF.



**Fig. 2.** (a) The initial biopsy from right ovary exhibited mainly solid pattern of growth. The tumor cells have rich, weakly eosinophilic cytoplasm, and mitotic figures are relatively frequent. (b) The second biopsy shows pleomorphic tumor cells in macrofollicular arrangement, (c) and numerous bizarre tumor giant cells, resembling those of choriocarcinoma, are observed. (d) Interspersed both intra- and extracellular hyaline globules are frequently found. H&E  $\times 100-250$

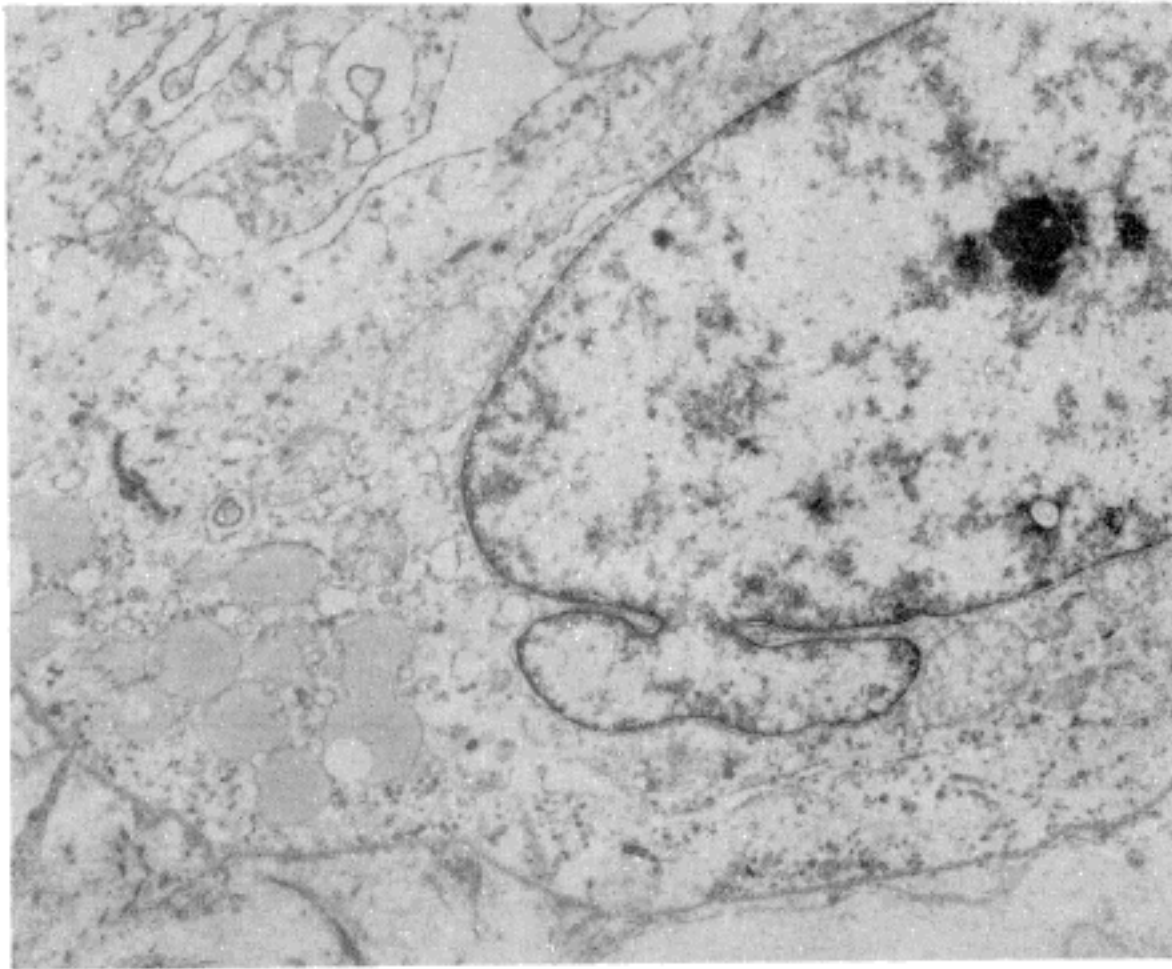
The cytoplasm of individual tumor cell was clear to weakly eosinophilic, and intracytoplasmic lipid was demonstrated on oil red-O staining. Both intra- and extracellular hyaline bodies were frequently observed (Fig. 2d). Immunohistochemical staining for HCG and alpha fetoprotein, using the peroxidase-antiperoxidase method gave a complete negative reaction.

**Ultrastructural findings:** The granulosa cells were closely apposed, and multiple small desmosomes connected individual cells. The cells were polygonal and occasionally surrounded by thin, interrupted basal lamina. The nuclei were oval and occasionally indented with a fine chromatin pattern.

The cytoplasm contained numerous microfilaments, a few lipid droplets, free ribosomes and slightly dilated endoplasmic reticulum. Mitochondria were moderate in number and not dilated.

## DISCUSSION

In the large series analysis of JGCT by Young et al.<sup>4)</sup>, the factors influencing the prognosis were the stage, size of the tumor, mitotic activity and degree of nuclear atypia. The clinical behaviour of the present case differs from ordinary JGCTs in its ① highly malignant clinical behaviour, ② disseminated multiorgan metastasis accompanying malignant



**Fig. 3.** The ultrastructural features of tumor cells showing indented nucleus, numerous intracytoplasmic microfilaments, lipid droplets, and desmosomes (arrows). ( $\times 9,000$ )

ascites in a short time interval, and ③ early recurrence. Based on the prognostic parameters of JGCT, unusually high mitotic rate and prominent pleomorphism of the present case may be partly responsible factors for an unfavorable prognosis.

The aforementioned pleomorphism has histopathological significance in that the JGCT can simulate malignant germ cell tumors morphologically, probably due to sequence of anticancer chemotherapy. The marked pleomorphism, with numerous giant cells closely resembling syncytiotrophoblasts and numerous hyaline globules made a pure histological differential diagnosis from a choriocarcinoma or endodermal sinus tumor impossible. Individual cell resembled a cytotrophoblast in their having vesicular nuclei and clear to weakly eosinophilic cytoplasm.

The findings contributory to the final diagnosis of JGCT included the followings:

1) The evidence of estradiol production by the tumor demonstrated by a marked, immediate fall in serum estradiol level after excision of the left ovary,

the isosexual pseudoprecocity with normal FSH and LH levels.

2) The characteristic follicular pattern of growth and luteinization of the individual cell.

3) Negative immunohistochemical reaction to HCG and alpha fetoprotein.

4) Ultrastructural evidence of granulosa cell differentiation, such as cytoplasmic microfilaments, basal lamina and intracytoplasmic lipid droplets.

Only on the basis of the above results of both ultrastructural and immunohistochemical analyses, an unequivocal diagnosis of JGCT was possible.

The cellular pleomorphism encountered in the present case is unique in three respects. First is the marked histologic difference between the two sequential biopsies despite relatively short time interval of 6 months. Second is the intervening chemotherapy, while the third is its association with highly aggressive clinical behaviour. The numerous multinucleated cells and atypical changes are well known features of chemotherapy-related histologic changes in some human tissue<sup>6)</sup>, and we believe that



it is quite possible that the pleomorphic change of this JGCT may be a sequence of chemotherapy.

Furthermore though the evidence is circumstantial, if the chemotherapy induced pleomorphism is related to more aggressive biologic behaviour, an ironic complication of ineffective chemotherapy will have been established.

If the pleomorphism is not a sequence of chemotherapy but an indigenous feature of the JGCT, all the findings including the unusually high mitotic rate and necrosis along with the pleomorphism of the present case should be added to the previously described histologic spectrum of JGCT. However, we prefer the former possibility because many classical cases of JGCTs reported previously did not touch on the findings we observed in this case.

#### ACKNOWLEDGEMENT

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#### — 국문 초록 —

#### 심한 다형성을 보인 난소의 Juvenile Granulosa Cell Tumor

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저자들은 임상적으로 짧은 기간내에 악성 결과를 받고 조직학적으로 심한 세포다형성을 보인, 10세 여아에 발생한 난소의 JGCT를 보고하는 바이다.

환아는 조속한 이차 성장을 보였고, 검사소견상 혈중 에스트라디올치의 증가가 관찰되었다. 종양은 우측 난소에서 발생하여 좌측 난소로 파급하였으며, 항암화학 요법에 불구하고 6개월 사이에 여러 장기로의 전이가 관찰되었다. 본 환아로부터 6개월간격으로 두 차례의 개복술을 통하여 얻어진 우측 및 좌측 난소는 상당한 조직학적 소견의 차이를 보인 바, 후자에서는 지금까지 알려진 연소기 과립 세포종의 소견과는 다른 다수의 종양 다핵거대세포들을 동반한 심한 세포다형성이 관찰되었다. 세포다형성에 관여하였을 만한 요인들에 대하여도 기술하였다.