Gonadoblastoma Overgrown by Dysgerminoma in Women with 46,XX Karyotype
-A Report of Two Cases-

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Gonadoblastoma is a neoplasm containing an intimate mixture of germ cells and elements resembling immature granulosa or Sertoli cells. It has been considered as in situ germ cell malignancy that can be overgrown by more malignant germ cell neoplasms. The tumor has been reported to almost exclusively develop in various types of gonadal maldevelopment syndromes containing the Y chromosome, such as in pure or mixed gonadal dysgenesis and, less commonly, in male hermaphroditism. However, occurrences in phenotypically and chromosomally normal, menstruating women are exceptionally rare. We report two cases of gonadoblastoma overgrown by dysgerminoma occurring in the ovaries of phenotypically and cytogenetically normal menstruating women. One of the two cases showed an area composed of granulosa cell tumor-like elements. This type of combination has been very rarely described, and exemplified that gonadoblastoma may progress to sex cord-stromal tumors as well as to the malignant germ cell tumors.

Key Words : Gonadoblastoma-Dysgerminoma-Sex Cord-Stromal Tumor-Gonadal Dysgenesis, 46,XX

In 1953, Scully described gonadoblastoma as a separate entity. It was defined histologically by the occurrence of discrete aggregates composed of germ cells and sex cord elements resembling immature Sertoli or granulosa cells.¹² The incidence of gonadoblastoma is high in patients with various gonadal maldevelopment syndromes containing the Y chromosome.⁵⁶ It is found in 25-30% of patients with XY gonadal dysgenesis, in 15-20% of 45,X/46,XY individuals,⁵⁶ and rarely in 46,XY male hermaphroditism patients.⁸ A small fraction of gonadoblastomas, however, develops in 46,XX females with no evidence of Y chromosomal DNA,⁹ in patients with histories of normal pregnancies or menstruation,²¹ and in phenotypically normal men with undescended testes.¹²¹ We report two cases of gonadoblastomas associated with dysgerminoma that occurred in phenotypically and cytogenetically normal menstruating women. The significance of this report is that it describes the rare cases of gonadoblastomas in the phenotypically and cytogenetically normal menstruating women and a rare case in which the gonadoblastoma, the malignant germ cell neoplasia and the sex cord-stromal tumor coexist in a same tumor.

CASE REPORT

Case 1

A 33-year-old unmarried woman was admitted to the hospital for evaluation of a low abdominal mass. The patient had received an evaluation for secondary amenorrhea one year before and was found to have bilateral cystic ovarian masses with multiple leiomyomas of the uterus. Her family history and past medical history were unremarkable. On physical examination,
the patient’s height was 160 cm and her weight was 90 kg. Breast development, pubic hair, and external genitalia were normal. A pelvic examination revealed an enlarged uterus with bilateral pelvic masses. She had had normal menstruation until one year prior to the examination revealing the pelvic masses. Her menstruations were moderate in amount, and they occurred at regular intervals. She had not been pregnant and denied having had any gynecological problems. An ultrasonography revealed septated multilocular cystic ovarian masses on both adnexa. Multiple small uterine leiomyomas were also identified.

An exploratory laparotomy revealed a 9.5 × 5 × 2 cm cystic right ovarian mass and a 5 × 4 × 4 cm left ovarian mass. There were multiple small subserosal leiomyomas in the uterus. The right ovary, the left ovarian cyst and the uterine myomas were removed. The right ovary was composed of an oligolocular cyst. The inner surface of the right ovarian cyst was hemorrhagic and shaggy, and the thickness of the wall ranged from 0.2 to 0.7 cm. There was an ill-defined firm, solid grayish yellow nodule, measuring 1.8 × 1.1 × 1 cm within the ovarian parenchyme (Fig. 1). The left ovary was cystic and had been ruptured previously. The inner surface of the left ovarian cyst showed red to brown patches without solid area.

Microscopically, bilateral ovaries showed the typical features of endometriotic cysts composed of an endometrial-type epithel-
lium, stroma, and hemosiderin-laden macrophages. The solid nodule in the right ovary was composed of three different histological features. There were gonadoblastomatous and dysgerminomatous areas (1.4 cm and 1.3 cm in greatest dimension, respectively) and a minor focus of a sex cord-stromal component (Fig. 1B). In the gonadoblastomatous area, discrete cellular nests were composed of intimately admixed germ cells and smaller epithelial cells resembling immature Sertoli or granulosa cells. The latter formed Call-Exner-like hyaline bodies. The germ cell components within the nests were similar to dysgerminoma which have large, round and vesicular nuclei, often with prominent nucleoli as well as abundant and clear, or eosinophilic, cytoplasm. A minor focus of sex cord-stromal components was seen at the periphery of the nodule, and the cells formed a trabecular or cord-like arrangement (Fig. 1C). The nuclei of these cells were oval or angulated; however, the grooves were inconspicuous, and significant pleomorphism and mitosis were absent. These cells surrounded circular spaces filled with eosinophilic hyaline materials and formed Call-Exner bodies.

Immunohistochemical staining for placental alkaline phosphatase (PLAP: 1:200, DAKO, Glostrup, Denmark) showed a strong positive reaction in the dysgerminomatous component and in the germ cell components of the gonadoblastomatous area. The sex cord-stromal elements resembling Sertoli or granulo-
ulosa cells in the gonadoblastoma were immunonegative for PLAP, but positive for inhibin (1:50, Serotec, Oxford, U.K.). The Ki-67 (1:200, DAKO) proliferation index was high in the germ cell components, but not in the sex-cord stromal elements.

The patient was treated with combination chemotherapy. Eighteen months later, she is well without evidence of recurrence or metastasis.

**Case 2**

A 30-year-old woman visited the emergency room because of abdominal pain. She had experienced normal menstruation with regular intervals, normal durations, and amount of blood. Her family history and past medical history were unremarkable. She had borne a healthy male baby two years before admission, and she had received dilatation and evacuation for artificial abortion several times after the last delivery. She was found to have a right ovarian mass. A right salpingo-oophorectomy was performed. The ovarian mass measured $8.5 \times 7 \times 5$ cm and the pedicle was distorted, resulting in a partly hemorrhagic parenchyme. The cut surface was mostly occupied by a well demarcated, pinkish gray colored solid mass, and there was a thin layer of normal appearing ovarian tissue beneath the surface (Fig. 2A). The fallopian tube was essentially normal.

The histologic findings in case 2 showed the typical features of gonadoblastoma overgrown by dysgerminoma. Most areas of the mass were replaced by dysgerminoma, with the gonadoblastomatous areas mainly identified at the periphery of dysgerminoma located beneath the surface of the ovary (Fig. 2B, C). After surgical treatment, we lost contact with her because she did not attend her regular follow-up visits.

Chromosomal analyses were performed with peripheral lymphocytes using conventional G-banding techniques. Both cases revealed normal 46, XX karyotypes (Fig. 3).

**DISCUSSION**

Neoplasms composed of germ cells and sex cord derivatives consist of two distinctive types: the gonadoblastoma and the unclassified type of mixed germ cell sex cord-stromal tumor. These two types have different histopathologic, genetic and endocrine features and different clinical and biological behaviors. Gonadoblastoma arises almost exclusively in the dysgenetic gonads of patients with a Y chromosome. The most common karyotypes of these patients are 46,XY and 45,X/46,XYmosaicism. It has been considered as in situ germ cell malginancy that commonly progresses to invasive germinoma or another type of malignant germ cell tumor, or rarely regresses with hyalinization and calcification. On the other hand, the mixed germ cell sex cord-stromal tumor usually occurs in phenotypically and cytogenetically normal females without any evidence of developmental abnormalities affecting the gonads, the external genitalia, or body fluids. These two types of neoplasms are sufficiently distinctive and usually do not coexist. In case 1, the tumor in which gonadoblastoma was overgrown by dysgerminoma was accompanied by an area showing a proliferation of sex cord-stromal elements. This feature is usually not seen in the gonadoblastoma or dysgerminoma. A combination of this type has very rarely been described, exemplifying that gonadoblastoma may be overgrown by the sex cord-stromal tumor as well as by the invasive germ cell tumors.

Both of the patients’ ovaries in case 1 were severely deformed with adhesions due to the endometriosis. Even though the characteristic features of the polycystic ovary were not observed and the serum levels of the luteinizing hormone (LH) and follicular stimulating hormone (FSH) were not measured prior to the operation, the secondary amenorrhea in case 1 might have been caused by the hormonal disorder associated with her obesity.

Phenotypic females with dysgenetic gonads and a Y chromosome are known to have an increased risk for gonadoblastoma and other malignant germ cell tumors. A minute Y-derived marker chromosome occasionally found in patients with gonadoblastoma suggests that there is a pathogenetic relationship between a gene on the Y chromosome and gonadoblastoma. The gene involved in the pathogenetic mechanism of gonadoblastoma is currently
unknown, but GBY (gonadoblastoma locus on Y-chromosome) and TSPY (testis-specific protein, Y-encoded) have been postulated to be candidate genes for the development of gonadoblastoma. The GBY gene, which is supposed to be distinct by location and function from the sex-determining region of the Y chromosome (SRY), has been putatively suggested to be located either adjacent to the centromere or on the proximal part of the long arm of the Y chromosome. The gene is postulated to have an undefined physiological function in normal males. In female, it is said to predispose dysgenetic gonads to develop malignant tumors. The pathogenetic mechanism for the frequent evolution of dysgerminoma in the background of gonadoblastoma also remains to be clarified. We could not perform DNA studies for the GBY gene in our cases, but the SRY genes of both patients were not demonstrated by polymerase chain reaction.

Dysgerminoma and gonadal dysgenesis in a 46,XX female with no evidence of Y chromosomal DNA have rarely been described. Cytogenetically normal patients who have gonadoblastoma may have the GBY gene on the X chromosome or on the autosomes. However, comprehensive research regarding the pathogenetic mechanism of gonadoblastoma occurring in phenotypically normal women is difficult to perform because the cases are very rare. Therefore, the centralization and collaborative study of the rare cases may be necessary in the future.

REFERENCES