PUBERTAS PRAECOX DUE TO OVARIAN TUMORS

SHOJI TANAKA

Ohuchi, Yamaguchi
(Received December 5, 1957)

From the pathologic and clinical points of view, one of the intriguing phases of gynecology is probably the study of unusual tumors of the ovary. *Von Kahlden*[1] in 1895 reported a patient with adenoma of the Craafian Follicle with transition to carcinoma. It has been generally agreed that this was the first authenic case of granulosa cell tumor. *Von Werdt*[2] in 1914 reported a tumor of the ovary as a granulosa cell type, but it was not until 1931 when *R. Meyer*[3] described 33 such cases that interest in study of these tumors was stimulated. Since then numerous papers have been reported as to these and other neoplasms, such as the adrenal and pineal, which cause unusual disturbance of the normal female function. It is not my desire to attempt to review completely the literature nor to discuss all of these tumors but rather to confine my discussion to the granulosa cell tumors of the ovary and report a case of precocious puberty.

Graunulosa cell tumor can no longer be considered a rare neoplasm. Because of the confusion in classification of earlier cases reported, it is almost impossible to estimate its incidence. As interest in these neoplasms increases, the incidence seems to increase. A granulosa cell tumor may be present at almost any age. The incidence of occurrence before puberty, however, is small. *Bland* and *Goldstein*[4] in 1934 collected 8 cases occurring under the age of 11 years, *Gross*[5] in 1940 reported 11 cases of patients under 10 years, and *Schultz*[6] in 1938 described 16 cases of ovarian tumors occurring at young children who have shown signs of precocious puberty.

The histogenesis of sex cell tumors of the ovary remains controversial subject. The older theory that the granulosa cells were derived from the germinal epithelium has been more or less discarded by the later theories of *Fischel*[7] and *Meyer*.[3]

From a gross pathologic standpoint, granulosa cell tumors assume a variety of appearances, depending upon their size and type. Some are soft and cystic while others are semisolid or solid, depending upon the amount of tumor tissue undergoing necrosis and resulting in the formation of cystic space. It is generally agreed that it is an ovoid solid, small, firm tumor. There is nothing characteristic in the gross appearance whereby one may know that he is dealing with a definitely malignant type of granulosa cell tumor, unless peritoneal metastasis or spread to other pelvic organs is found at operation. There is also a variability in the microscopic pattern. It is exhibited not only in different tumours but in one and the same tumour, in different parts. It therefore seems to be of importance that numer-

ous blocks are studied in order to derive an intelligent impression of the tumor as a whole. The main histologic types have been described in detail by many authors as follicular, cylindromatous, trabecular, and diffuse.

Malignancy is still a moot question in the study of these tumors. The tumor is often called granulosa cell carcinoma and yet *Karsner*[8] states that even the gloomy statistics, unlike the data of other internal carcinomas, admit of cure in 62 per cent of the cases. He also states that it is not good practice to consider a tumor malignant merely because of its potentiality, and no more justifiable to call all granulosa cell tumors carcinomas than to classify under this same heading the mammary adenoma, the papilloma of the bladder, and other similar lesions.

In 1934 *Novak* and *Brawner*[9] described that the clinical malignancy rate was 28.1 per cent of 32 cases. Recently *Norris* and *Dunne*[10] reported a series of 24 cases, of which 10 or 45.8 per cent survived and all having remained well varying from a period of two to twenty-two years. It seems likely, therefore that as in many other tumors the grades of malignancy have to be considered, although Novak believes that it is not as yet possible to base these on histologic criteria. Postoperative deep x-ray therapy is not universally considered a necessity. Many feel that x-ray therapy should be reserved for the treatment of reccurrence, as it is a well-established fact that the granulosa cells are quite radioactive.

Acculate hormonal studies on these tumors are still relatively infrequent. This is probably due to the fact that the diagnosis is made only on pathologic examination when it may be too late for hormonal studies to be of value.

The clinical characteristics, as in other ovarian neoplasms, depend upon whether they are large enough to cause pain and disconfort. The more distinctive symptomatology is dependent upon the capability of the tumor cells to produce the estrogenic hormone. During the female reproductive period, because the secondary sex characteristics have long since been developed, there is no definite change, and the tumor merely adds quantitatively to the cyclical hormonal content of the blood. Tumors occurring during the postmenopausal age, when very little estrongenic hormone is found in the blood, produce re-establishment of periodic menstruation-like bleeding and also hypertrophy of the uterus. There is no demonstrable effect upon the secondary sexual characteristics. This is probably due to unreceptivity during this period. With removal of the tumor at this age, the abnormal menstration ceases. *Novak* and *Dworzak*[11] recently observed a patient who experienced a second menspause from the standpoint of vasomotor phenomena after removal of the growth. When these tumors occur during childhood, before inauguration of the normal estrogenic function, the clinical manifestations of frecocious puberty are evoked. Removal of the tumor, whether it be frimary or reccurrent, is followed by regression of all these symptoms. Granulosa cell tumors have been reported which have produced no vaginal bleeding in spite of a marked increase in estrogenic excretion. It can definitely be stated that the

freseuce of frecocious puberty with a definite ovarian enlargement is strongly suspicious of a granulosa cell tumor. During active sex life the bleeding may be fresent only in the form of irregularity of the meustration so that the preoperative diagnosis can only be suspected. In the postmenopausal state, the reccurrence of vaginal bleeding associated with an adnexal mass should make one at least suspicious of a granulosa cell tumor.

Recently there has come under my observation a child at 25 months, who had the above mentioned symptoms. The diagnosis of granulosa cell tumor was made which proved to be a simple follicular cyst of the ovary, I would like to report this case in detail.

A Report of Case

T. U., 25 months of age, was referred by some physician who first attended the child when she was five weeks old. She was seen at irregular intervals during the following year and from the age 9 months until 17 months, no medial attention was required. At fourteen months of age, she was in an excellent of nutrition. She could sit, stand, walk with help, and was alert and happy. It was at this time that enlargement of the labia and the presence of pubic hair was first noticed. On rectal examination it was thought that the left ovary was enlarged to about the size of the end of a thumb. There were no breast changes demonstrated. In February, 1955, the mother noticed some vaginal discharge and some blood in the urine. Urinanalysis at that time revealed the presence of red blood cells. Because there had been no rapid progress in development of the secondary sex characteristics, she was referred to me for examination. The mother stated that when the child was 17 months of age she was more restless and irritzble that usual. This period of irritability which occurred in June, persisted for three days, after which time the patient seemed better. Again in August and September the patient underwent two successive periods of restlessness and irritability, during which time blood was again noticed in the urine. There had been very little development of the breasts and no increase in the amount of pubic hair. Rectal examination revealed a definite enlargement of the left ovary. A tentavie a diagnosis of granulosa cell tumor of the left ovary was made and operation advised. On Nov. 25, 1955 operation was performed under general anaesthesia. A left paramedian incision was made with exposure of the peritoneal cavity, revealing an enlargement of the left ovary, part of which was a very thin-walled cyst. The uterus was not perceptibly enlarged and the right ovary seemed to be nomal. A left salpingo-oophorectomy was performed. This patient made as uneventful recovery and was discharged from the hospital on the tenth postoperative day.

The specimen was sent to the laboratory of examination. The report was as follows:- Gross; The specimen in formalin consisted of a small 3 by 1 by 1 cm. fragment of ovary which contained many small cysts filled with a clear fluid.

One end of the ovary was missing, this having been removed for examination. Microscopically; There were a few premordial follicles in the cortex of the ovary which was extremely narrow and surrounded the tumor. The tumor for the most part consisted of regular, small, polygonal or ova, cells with even, regular, oval, vesicular nuclei, some in division. These cells appearing like granulosa cells formed a variety of patterns, some solid, some cystic. Surrounding the nodules of granulosa cells was a loose stroma of connective tissue which was reticular and traversed by a number of small, delicate capillaries and contained cells with small deeply-straining oval nuclei which were scattered throughout, chiefly at the periphery in small groups of four to a dozen or more. They suggested a derivation from the granulosa cells, comprisong the main tumor. In other fibrous areas where these small cells were not as numerous, the connective tissue stroma appeared somewhat more condenced and apparently older. Different areas of the tumor showed a diffuse variety, a finely folliculoid pattern, and in place a cystic pattern. A considerable amout of lipoid was present in the granulosa cells and in the cells extending into the loose stroma Surrounding the typical granulosa cell areas. The appearnce of the tumor suggested the development of follicles and their attempted transformation to corposa lutea and finally to corpora fibrosa.

The patient was seen within the last month and seems to be well in every respect. There have been no further signs of recurrence either in symptoms or upon physical examination.

SUMMARY

One case of ovarian tumor associated with precocious puberty is reported in this communication. It is considered to be a typical granulosa cell tumor.

From a review of the literature and a study of my case, I have no doubt that important advancemnts will be made, particularly with regard to the hormonal studies of this group of neoplasms.

Functioning tumors of the ovary which were formerly unrecognized, today represent a subject of such broad possibilities as to be of interest to the medical profession in general. From an endocrinologic viewpoint, these tumors furnish definite evidence of hormonal production and its clinical effects. To the embryologist, the various phases of cellular didderentiation are of especial interest. The identification of these unusual tumors stirs the interest of the internist. The pathologist's, as well as the surgeon's interest is concentrated upon the difficult problem of confirming the clinical diagnosis and choosing a proper course of treatment. The general interest in the study of these tumors has been stimulated to such a degree that a positive diagnosis is more likely in the majority of cases. Consequently, through proper diagnosis, pathologic confirmation and proper treatment, the prognosis today is more favorable than in the past.

Acknowledgment: I would like to thank to Dr. H. YAGI of Okayama for his advice.

REFERENCES

1) VON KAHLDEN, C.: *Zentralbl. f. allg. Path. u. Path. Anat.*, **6**: 257, 1895.
2) VON WERDT, F.: *Beitr. z. path. Anat.*, **59**: 593, 1914.
3) MEYER, R.: *AM. J. Obst. & Gynec.*, **22**: 697, 1931.
4) BLAND, P. B., and GOLDSTEIN, L.: *Surg. Gynec. Obst.*, **61**: 250, 1935.
5) GROSS, R. E.: *AM. J. Dis. Child.*, **59**: 579, 1940.
6) SCHULZE, M.: *AM. J. Obst. & Gynec.*, **26**: 627, 1933.
7) FISCHEI, A.: *Wien. med. Wchushr.*, **51**: 2226, 1924.
8) KARSNER, H.T.: *Trans. Coll. Physicians* **17**: 301, 1940.
9) NOVAK, E., and BRAUNER, J.N., JR.: *AM. J. Obst. & Gynec.* **28**: 637, 1934.
10) NORRIS, C.C., and DUNNE, F.S.: In Press.
11) NOVAK, E.: *Gynecological and Obstetrical Pathology*, 1940.