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Gonadoblastoma and Dysgerminoma Associated with 46,XY Pure Gonadal Dysgenesis

— A Case Report —

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Gonadoblastoma and dysgerminoma developed in a 24-year-old phenotypic female patient with 46,XY pure gonadal dysgenesis. This patient presented with primary amenorrhea. Clinical characteristics showed a typical stigmata of gonadal dysgenesis: primary amenorrhea, sexual infantilism, a small uterus and bilateral streak gonads. A 46,XY karyotype was made by lymphocyte culture. The patient was counseled to undergo a prophylactic bilateral gonadectomy, but she refused. Three years and three months after the initial diagnosis she felt a growing pelvic mass. Bilateral gonadectomy and total hysterectomy were performed. Histological examination revealed gonadoblastoma and dysgerminoma on both gonads. After surgery the patient received radiation therapy and also was started on hormone replacement therapy. Two years and two months after treatment by surgery the patient is well and free of recurrence.

Key Words: *Gonadoblastoma, Dysgerminoma, 46,XY Pure Gonadal Dysgenesis, Gonadectomy*

INTRODUCTION

In humans the X and Y chromosomes carry the major determinants necessary for male and female gonadal development. Gonadal dysgenesis can occur in individuals with apparently normal male (46,XY) or female (46,XX) chromosomal complements. 46,XY pure gonadal dysgenesis, also known as Swyer syndrome, is a disorder of sexual differentiation (Swyer, 1955). Its characteristics include a female phenotype without the somatic stigmata of Turner's syndrome, primary amenorrhea, sexual infantilism and bilateral streak gonads. Because of the relatively high probability of gonads undergoing neoplastic transformation, their prompt removal should be performed in all patients with XY gonadal dysgenesis (Grumbach and Van Wyk, 1974). In this paper we report a case of gonadoblastoma and dysgerminoma arising in a patient with 46,XY gonadal dysgenesis.

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CASE REPORT

An unmarried 21-year-old phenotypic female presented with primary amenorrhea in January 1988. Birth and childhood presented no particular features. Her medical and surgical histories were unremarkable. There was no family history of primary amenorrhea nor was there sexual ambiguity. She had developed pubic hair at age 14. Physical examination revealed the patient to have a tall stature and retarded puberty. Blood pressure was 110/70 mmHg, height 170 cm, weight 63 kg. Her breast development was retarded. The pubic and axillary hair was scanty. No mass was palpable in either inguinal region. Pelvic examination revealed a hypoplastic labia and slightly hypertropic clitoris. The vagina, 7cm in length, was normal. The cervix

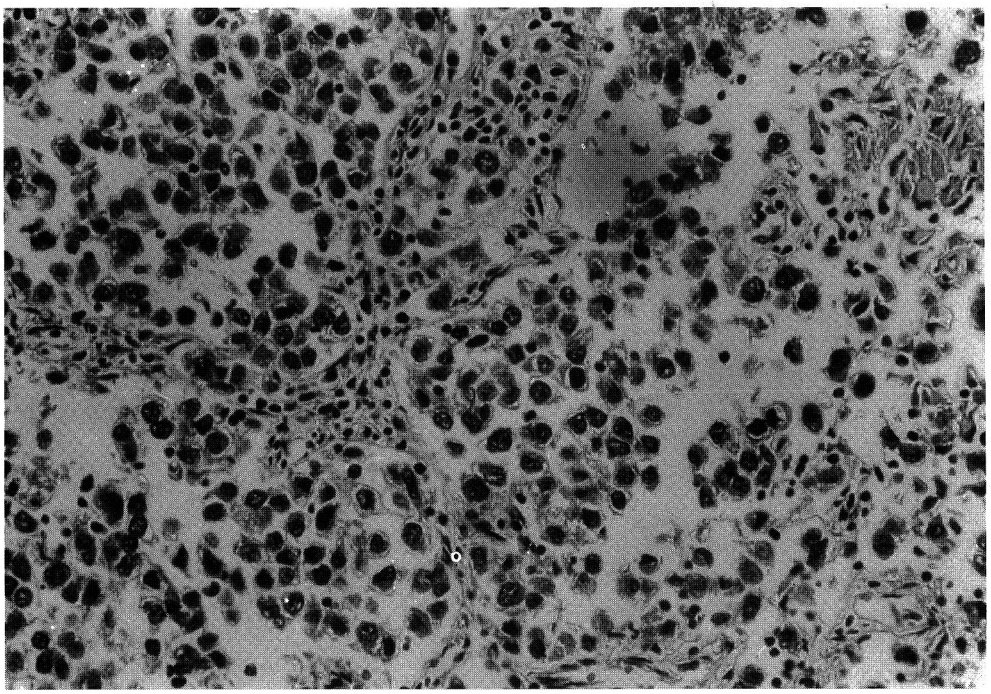

Fig.1. Photomicrograph of the dysgerminoma showing uniform aggregates of primordial germ cells surrounded by delicate strands of connective tissue and lymphocytes. (H & E, x 200).

was infantile and the uterus was rather small. Neither adnexae were palpable. Peripheral lymphocyte culture from two independent samples showed a 46,XY karyotype. A small uterus without gonads was suggested by pelvic ultrasound examination. A tentative diagnosis of 46,XY pure gonadal dysgenesis was made. The patient was counseled to undergo a prophylactic bilateral gonadectomy. But she refused and was lost to follow up.

She visited our hospital again three years and three months after initial diagnosis because she had felt a mass growing in her lower abdomen. A semisolid mass measuring $10 \times 9 \times 8$cm was found by ultrasonographic examination. The serum level of FSH was elevated to 50.48 mIU/ml. Other hormonal profiles were within the normal range for adult females: estradiol (10 pg/ml), progesterone (0.1 ng/ml), 17 -hydroxyprogesterone (0.36 ng/ml), testosterone (0.11 ng/ml), cortisol at 8 A.M. (8.14 μg/dl), DHEAS (76.62 μg/dl), LH (11.78 IU/ml), prolactin (5.36 ng/ml). The levels of serum tumor markers prior to surgery were within the normal range: AFP (7.22 ng/ml), beta HCG (1 mIU/ml), CEA (2.25 ng/ml), CA 125 (31.84 U/ml). Routine laboratory values were all within the normal range. X-ray of the chest was normal.

At the time of laparotomy, about 200ml of straw colored ascitic fluid were aspirated. The uterus was hypoplastic but both fallopian tubes showed a normal appearance. Bilateral masses in both adnexal areas were found. On the right side, the mass measured about $12 \times 8 \times 5$cm, was of hard consistency and was multinodular. Its surface was pinkish-tan and smooth. The mass on the left side was smaller ($5 \times 5 \times 4$cm) than the right one, again with a smooth, pinkish surface. A total hysterectomy with bilateral gonadectomy was performed. There were no signs of metastasis in the pelvis or abdomen.

Postoperative abdominal CT showed no evidence of abnormal lymphadenopathy in the abdomen and retroperitoneal space. Intravenous pyelogram showed no abnormal findings. On histological examination, the bilateral ovarian masses were predominantly composed of pure dysgerminoma characterized by large aggregates of uniform primordial germ cells surrounded by delicate strands of connective tissue containing lymphocytes (Fig.1). Focally there were cellular nests

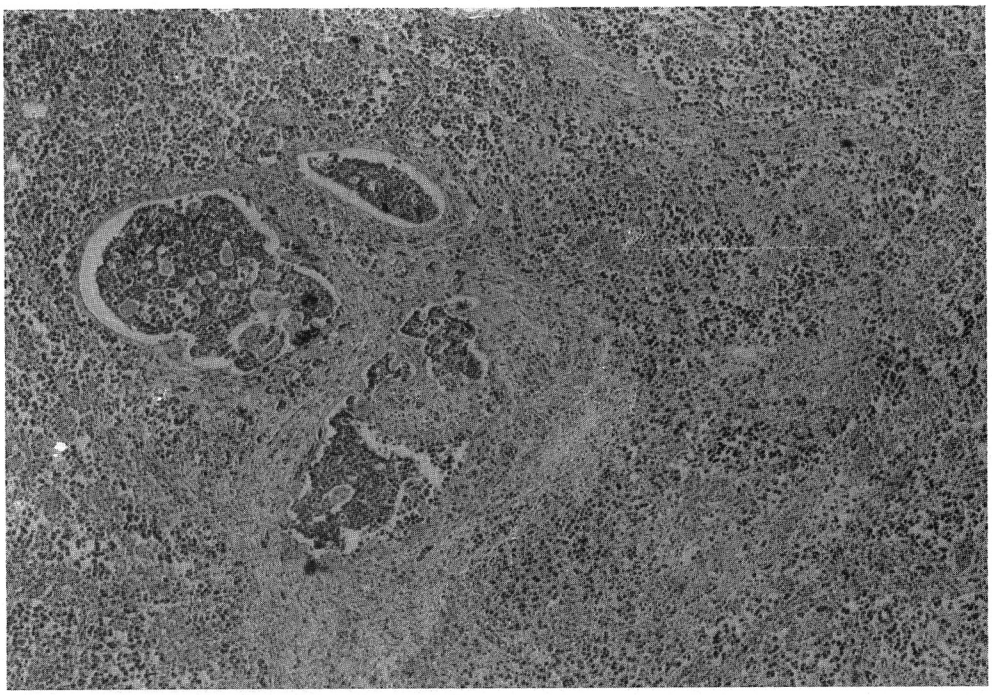

Fig. 2. Photomicrograph showing a focal gonadoblastomatous area characterized by cellular nests containing a mixture of germ cells and sex cord derivatives (H & E, x 40).

containing a mixture of germ cells and sex cord derivatives resembling immature Sertoli or granulosa cells, suggesting the presence of foregoing gonadoblastoma (Fig.2). The tumor had penetrated the ovarian capsules and infiltrated into the adjacent structures with multiple tumor emboli in the vascular structures. The cytologic report for ascitic fluids showed no malignant cells.

The patient received postopearative radiation therapy to the whole abdomen and pelvis in doses of 2520 cGY within an overall period of four and a half weeks.

Currently, the patient is being treated with cyclic administration of 2 mg of estradiol valerate in combination with 10 mg of medroxyprogesterone acetate.

DISCUSSION

Individuals with 46,XY pure gonadal dysgenesis show female external genitalia, a uterus and fallopian tubes. At puberty, secondary sexual development fails to occur. The height is normal and somatic anomalies usually do not coexist in this disorder. Both sporadic as well as familial cases have been reported (Berg et al., 1989).

The pathogenesis of XY gonadal dysgenesis involves a deficit in the production, regulation or expression of the testicular-determining factor (TDF) believed to be located on the Y short arm (Muller, 1987). This may induce loss of testicular tissue before 7 to 8 weeks of embryogenesis. The sex-determining region (SRY) of the Y chromosome has properties expected of the TDF (Berta et al., 1990; Sinclair et al., 1990). The SRY gene is present in some patients with XY gonadal dysgenesis (Behzadian et al., 1991; Tsutsumi et al., 1993) and absent in others (Disteche et al., 1986; Levilliers et al., 1989). We did not type the histocompatibility (H-Y) antigen in this patient.

Determination of H-Y antigen would be of no clinical relevance in patients with XY gonadal dysgenesis (Berg et al., 1989).

A dysgerminoma or gonadoblastoma occurs in 20% to 30% of individuals who have gonadal dysgenesis and a Y chromosome (Simpson and Photopulos, 1976). Often the neoplasia arises in the first or second decade. The mean age at diagnosis of the neoplasms arising in dysgenetic gonads was 18.6 years, with 94 percent of the patients being less than 30 years of age, 62 percent less than 20, and 9.8 percent below the age of 10. In one

instance, the neoplasm was discovered at the age of 6 months (Troche and Hernandez, 1986). The risk of malignancy in patients with gonadal dysgenesis and a Y chromosome component is 16% at the age of 20 and of 27.5% at the age of 30 (Manuel et al., 1976). Therefore prophylactic bilateral gonadectomy is regarded as necessary as soon as possible. A hysterectomy is usually offered during gonadectomy to patients with XY gonadal dysgenesis to prevent endometrial carcinoma in a functionless uterus. Recently there have been many successful pregnancies achieved through ovum or embryo donation in these individuals without gonads (Frydman et al., 1988; Sauer et al., 1989). Thus the uterus can be preserved if the patient desires future childbearing. Recently the gonadectomy, previously performed during laparotomy, can be attempted via a laparoscopic approach. Many reports have confirmed that laparoscopic gonadectomy is a safe, cost-effective and simple procedure (Droesch et al., 1990, Shalev et al., 1992; Wilson et al., 1992). Since ovarian dysgerminoma is one of the most radiosensitive human cancers and in view of the low recurrence tendency in patients treated with surgery and postoperative radiation therapy, prophylactic irradiation is considered to be the most appropriate procedure (La Polla et al., 1987; Shabbir et al., 1991). Berg et al (1987) have reported postoperative radiotherapy in two sisters with 46,XY pure gonadal dysgenesis and gonadoblastoma/dysgerminoma. They underwent hysterectomy and bilateral gonadectomy. Following surgery, the patients received low pelvic irradiation at a dose of 3,000 cGY. Five years after treatment both patients were free of recurrence. Our case report emphasizes that surgical exploration and bilateral gonadectomy should be performed without undue delay in patients with gonadal dysgenesis and Y chromosome. Careful follow up with periodic pelvic examination and ultrasonography is needed in these patients if they refuse removal of abnormal gonads.

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