Swyer syndrome, 46,XY gonadal dysgenesis, a sex reversal disorder with dysgerminoma: a case report and literature review

Jing Zhu, Xishi Liu, Hongyan Jin, Xin Lu

Obstetric and Gynecology Hospital at Fudan University, Shanghai (China)

Summary

Background: Swyer syndrome, 46,XY gonadal dysgenesis, is a sex reversal disorder with a female phenotype. Germ cell tumors, including dysgerminoma, may arise in streak gonads of patients with gonadal dysgenesis. *Case:* A 22-year-old female patient with a 46,XY karyotype was admitted to hospital for primary amenorrhea and a pelvic mass. Laparotomy exploration revealed a hypoplastic uterus and a 80 × 70 × 60 mm mass in the right gonad with extension to the pelvic peritoneum. Histologic finding in frozen section was dysgerminoma. Debulking surgery with pelvic lymphadenectomy was subsequently performed and the patient was given four cycles of chemotherapy (bleomycin, etoposide, and cisplatin) post-operation. *Conclusion:* The presence of Y chromosome in patients with 46,XY gonadal dysgenesis may increase the risk of gonadal tumors. A prophylactic bilateral salpingo-gonadenectomy should be advised to those patients.

Key words: Swyer syndrome; Gonadal dysgenesis; Dysgerminoma.

Introduction

The XY gonadal dysgenesis is a sex reversal disorder and the result of embryonic testicular regression sequences. Pure XY gonadal dysgenesis, Swyer syndrome, has a 46,XY karyotype and streak gonads. Most of those phenotypically females present with primary amenorrhea, female type infantile external genitalia, normal stature, and normal Müllerian structures. Mutations in the sex-determining region on the Y chromosome (SRY) gene are found in this syndrome.

Dysgerminoma is occasionally seen in patients with gonadal dysgenesis. About 5% of dysgerminomas are found in phenotypic women patients with chromosomal abnormalities such as 46,XY or 45,X/46,XY mosaic. For those patients, dysgerminomas often arise in benign gonadolblastomas [1]. Therefore, whether the karyotype shows the presence of a Y chromosome, it still has the risk of malignancy developing from the abnormal gonads [2].

We report a case with 46,XY karyotype which resulted in dysgerminoma. The literature is reviewed to discuss the necessity of preventive gonadectomy in order to decrease the risk of gonadal malignancy.

Case Report

In May 2009, a 22-year-old phenotypically female individual was admitted to the Obstetrics and Gynecology Hospital of Fudan University for primary amenorrhea. The physical examination revealed normal breast development, absence of axillary hair, infantile female-type external genitalia, and sparse pubic hair. The vagina, 6 cm in length, was explored. The rectal examination revealed a rudimentary cervix and uterus. An irregular, fixed, solid pelvic mass on the right side was palpable. Endocrinological studies revealed elevated follicle-stimulating hormone (FSH, 97.75IU/l), with normal range of estradiol (58.5 ng/l), testosterone (1.29 nmol/l) and prolactine (18.47 ug/l). Adrenal function was normal. Tumor marker examination revealed a slightly elevated α-fetoprotein (AFP, 11.16 ng/ml, normal value, < 10 ng/ml) level, while the other tumor markers were all in normal ranges (CA125: 27.80 u/ml, CA153: 3.80 u/ml, CA199: 4.68 u/ml, CEA: 0.52 ng/ml, lactic dehydrogenase, LDH: 202 U/l). Pelvic ultrasound examination indicated a pre-pubertal uterus and a solid mass the size of 79 × 68 × 64 mm. Computed tomography (CT) scan showed absence of the uterus, and gonads of normal size in the pelvis, and neither testis in the inguinal canal. The peripheral blood karyotype was 46, XY. The patient was diagnosed with gonadal dysgerminoma with Swyer syndrome, thus surgical treatment was planned.

Laparotomy exploration showed a hypoplastic uterus, long slender fallopian tubes, a streak gonad on the left, and a gray/white, nodular neoplasm in the right gonad, measuring 8 × 7 × 6 cm in diameter with implants on the right pelvic peritoneal surface. No metastasis was found in the posterior cul-de-sac, paracolic gutters, right hemidiaphragm, liver capsule, omentum, bowel serosa and its mesenteries. There was no pelvic or paraaortic lymphatic dissemination. Histologic finding in frozen section was dysgerminoma (right gonadal and right pelvic peritonium). Then total abdominal hysterectomy, bilateral salpingo-gonadectomy, infracolic omentectomy, resection of peritoneal metastases, and pelvic lymphadenectomy were performed. Final histologic examination demonstrated right gonadal dysgerminoma with Swyer syndrome (complete form), FIGO Stage IIc.

Following the cytoreductive surgery, four cycles of combined chemotherapy was given, BEP (bleomycin, etoposide, and cisplatin). The patient is disease free after two years of follow-up.

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Fig. 1a

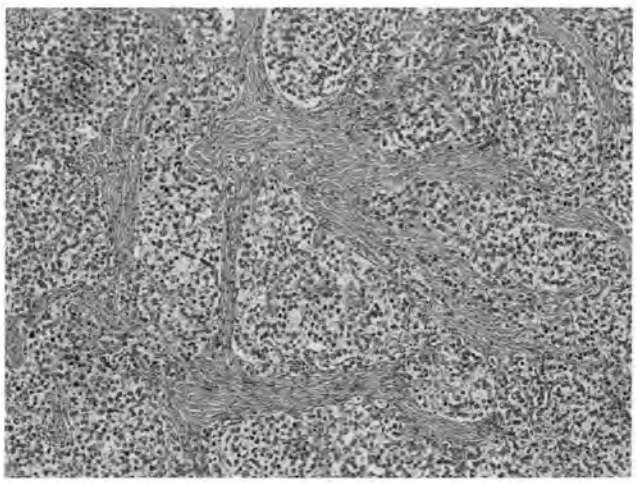

Fig. 1b

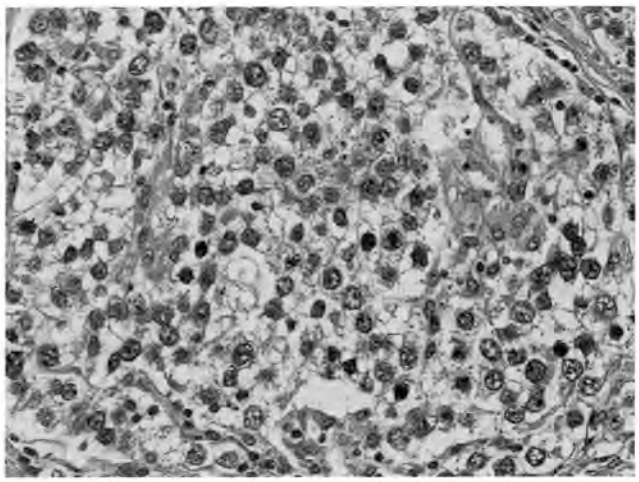

Fig. 1c

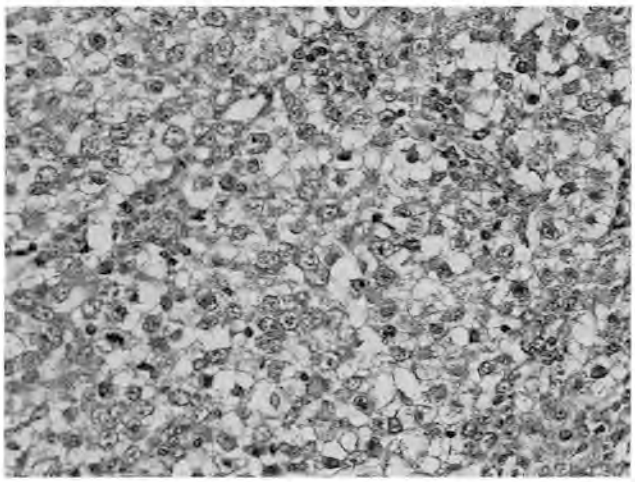

Fig. 1d

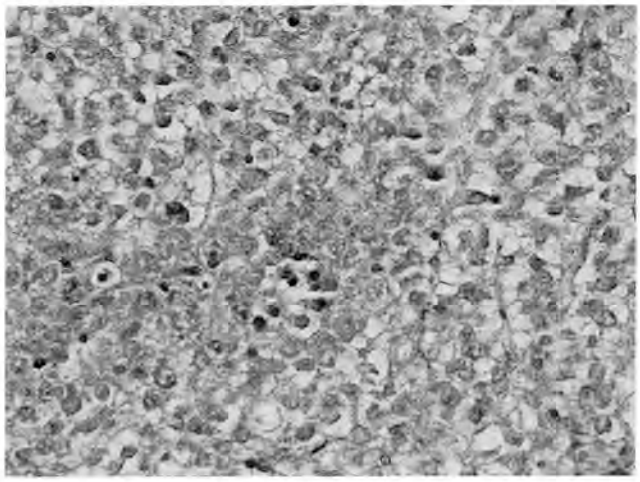

Figure 1. — Histologic finding of tumor tissue from the right gonad of the patient:
a) H&E stain (original magnification ×100);
b) H&E stain (original magnification ×200);
c) Immunohistochemical stain, HPL positive immunoreactivity;
d) Immunohistochemical stain, HCG positive immunoreactivity.

Discussion

Individuals with Swyer syndrome (complete form) usually present an unambiguous female-type external genitalia, hypoplastic uteri, bilateral streak gonads, a 46,XY karyotype and hypergonadotropic hypogonadism. Germ cell tumors, like gonadalblastoma, arise in streak gonads in 30% of XY sex-reversed patients [3, 4]. In some cases, gonadoblastoma can develop into dysgerminoma [5]. Thus it is hypothesized that the expression of the Y chromosome in these patients increases the high risk factor of developing gonadal tumors, such as gonadoblastoma or dysgerminoma. The testis-determining gene *SRY* is a Y-chromosome gene essential for testicular development. The incidence of gonadal tumor formation in patients with *SRY* abnormalities was 50%. And the result of the meta-analysis concerning the relationship between *SRY* aberrations and gonadal tumor formation has shown that benign and malignant gonadal tumors were observed in 21 out of 40 (52.5%) patients with *SRY* abnormalities [6]. Funato *et al.* suggested that somatic mutations of multiple genes might involved in dysgerminoma of patients with pure gonadal dysgenesis [7].

We have reviewed 22 available reported cases of XY gonadal dysgenesis with gonadal tumors since 1993 (Table 1) (6 cases published in Chinese, 14 cases published in English) [7-18]. Among 22 cases the age was from a month to 28 years old in variation; 14 cases were karyotype 46,XY, seven cases were 45,X/46 XY, and there were one a true hermaphroditism 46,XX/46,XY. Of 14 patients with karyotype 46,XY, two dysgerminomas, four gonadoblastomas, five gonadoblastomas with dysgerminomas, two gonadoblastomas with mixed germ cell tumors, and one yolk sac tumor (YST) were found. Of seven patients with karyotype 45,X/46,XY, six gonadoblastomas and one gonadoblastoma with dysgerminoma were reported. A patient with karyotype 46,XX/46,XY had dysgerminoma. The size of the tumors varied from a minimal lesion in a streak gonad to a mass measuring 14 cm in diameter. The rearing gender of most

Table 1. — *Literature summary of gonadal tumors with the presence of a Y chromosome.*

Reference	Country	Age	Complaint	Karyotype	Treatment	Pathology	Prognosis
Lou Liandi, *et al.* 1993	China	3 yr		45,X/46,XY	hysterectomy and bilateral annessectomy	GB with sertoli cell tumor	ND
		8 yr		45,X/46,XY	hysterectomy and bilateral annessectomy	GB	ND
		24 yr		45,X/46,XY	hysterectomy and bilateral annessectomy	GB	ND
Chen M.J., *et al.* 2005	Taiwan, China	18 yr		46,XY	bilateral gonadectomy	GB with malignant mixed germ cell tumor	Follow-up 13 yr, disease free, a pregnancy with donor oocyte
Jin Lina, *et al.* 2007	China	18 y	primary amenohrrea	46,XY	bilateral gonadectomy	GB	ND
		20 yr	primary amenohrrea	46,XY	bilateral gonadectomy	GB	ND
		+24 yr	primary amenohrrea	45,X/46,XY	hysterectomy and bilateral annessectomy	GB	ND
		28 yr	primary amenohrrea	46,XY	right gonadectomy	GB	ND
Joki-Erkkilä M.M., *et al.*2002	Finland	16 yr	primary amenohrrea	46,XY	bilateral annessectomy	GB with focal malignant DG	Follow-up 12 mo, disease free
Morerio C *et al.* 2002	Italy	11 yr	abdominal mass	46,XY	bilateral annessectomy, and chemotherapy	DG	ND
Tanaka Y. *et al.* 2000	Japan	17 yr	mass, lower abdominal	20% 46,XX/80% 46,XY	right salpingo-oophorectomy, left ovarian wedge resection, and omentectomy, and chemotherapy	DG	Follow-up 9 mo, and a pregnancy in term
Handa Y., *et al.* 1995	Japan	17 mo	mass	46,XY	Excision of the right testicular tumor, and the left orchiectomy, and chemotherapy	YST	Follow-up 4 yr, disease free
Hong JR *et al.* 1995	USA	38 mo	multiple congenital anomalies	46,XY	bilateral gonadectomy	GB	ND
Love JD *et al.* 2006	USA	17 yr	nephrotic syndrome and progressive renal failure, primary amenorrhea	46,XY	bilateral gonadectomy, and chemotherapy	left GB+ right DG	ND
Caponetti G *et al.* 2006	Italy	19 yr	primary amenohrrea	46,XY	total hysterectomy, annessectomy, pelvic and para-aortic lymphadenectomy, and chemotherapy	GB+ a mixed tumor composed of malignant teratoma (50% of the tumor), chondrosarcoma (10%), neuroglial cancer (10%), dysgerminoma (b5%) and yolk sac tumor (20%)	2 yr after a histologic diagnosis of GB, a mixed germ cell tumor developed, then 6 mo after surgery, progression occurred, 3 mo later, died
Kildal W *et al.* 2003	Norway	16 yr	abdominal pain	46,XY	bilateral oophorectomy and the pelvic tumors	left DG+ right DG+GB	Follow-up 3 yr, no progression
Alonso RP *et al.* 2005	Mexico	1 mo		45,X/46,XY	bilateral gonadectomy and internal genitalia	focal GB	ND
		11 mo		45,X/46,XY	biopsy	GB	ND
		2 mo		45,X/46,XY	bilateral gonadectomy	GB	ND
		28 mo		46,XY	gonadectomy	GB	ND
		15 yr		45,X/46,XY		right DG with burned out GB+ left GB with focal transformation to DG	ND
Funato T. *et al.* 2002	Japan	15 yr	primary amenorrhea and an intra-pelvic mass	46,XY	bilateral gonadectomy	DB+DG	ND
		18 yr	primary amenorrhea	46,XY	bilateral gonadectomy	left DB+DG+ right GB	ND

GB = gonadoblastoma; DG = dysgerminoma; ND: no data.

Table 2. — *Gonadal dysgenesis: patients with germ cell tumors.*

Karyotype histology	DG	GB+DG	GB
46,XY*	2	5	4
45,X/46,XY	0	1	6
46,XX/46,XY	1	0	0
Total	3	6	10

GB = gonadoblastoma; DG = dysgerminoma.
*2 cases of gonadoblastoma and malignant mixed germ cell tumor with karyotype 46,XY a YST with karyotype 46,XY.

patients was female, except a two-month and a eight-year old boy karyotyping 45,X/46, XY. The tumors of 11/20 patients were unilateral and 9/20 were bilateral (no description in the other two cases).

In the literature, primary amenorrhea was the main reason for medical consultation, and lower abdominal pain and pelvic mass were also the chief complaints. The external genitalia of the patient in our report was unambiguous female type with immature vulva lacking pubic hair, while in the other reports a slight clitoromegaly or immature vulva was usually described. LDH was found to be elevated in patients with ovarian dysgerminoma and dropped after treatment. In the literature, a dysgerminoma, a gonadoblastoma, and a YST patient with elevated LDH were reported. The LDH remained at a normal level in our case.

The treatment of patients with XY gonad dysgenesis with gonadal mass was primarily surgical. As shown in Table 1, unilateral or bilateral salpingo-gonadetomy, hysterectomy and bilateral salpingo-gonadectomy, or a tumor debulking with or without pelvic and paraaortic lymphadenectomy were undertaken in the those patients. In patient with YST an excision was performed of the right testicular tumor and left orchiectomy. Surgical staging was undertaken for the present case. The FIGO staging was IIc. Tumor debulking and pelvic lymphadenectomy were performed.

Chemotherapy should be regarded as an option for the treatment of gonadal malignancies. For patients with Stage I dysgerminoma, no additional chemotherapy is indicated. However, patients with advanced stage disease require adjuvant treatment with bleomycin, etoposide and cisplatin [19]. In the literature, the following chemotherapeutic regimens have been recommended: BEP (bleomycin, etoposide, and cisplatin), VBP (vinblastine, bleomycin, and cisplatin), VAI (vincristine, actinomycin, and iphosphamide), EP (etoposide and cisplatin) [20, 21]. In addition, dysgerminomas are also radiosensitive. Panel radiotherapy was the adjuvant treatment option, but now it is reserved for patients with recurrent or chemoresistant disease.

Survival rate for patients with the disease varied according to the stage at operation and the subsequent treatment. Of all 22 cases in the literature we reviewed, prognosis information was only recorded in six cases. Follow-up time varied from a year to 13 years. A 46,XY gonadal dysgenetic female with gonadoblastoma and malignant mixed germ cell tumor underwent bilateral gonadectomy, and had been free from recurrence for 13 years [8]. As for another four case reports, the patients with gonadal gonadoblastoma and dysgerminoma (a patient with YST) showed no sign of recurrence after surgery (with or without adjuvant chemotherapy). Two patients achieved successful pregnancies (one through oocyte donation and IVF programme) [8, 12]. However, one case of gonadal dysgenesis XY female type with gonadoblastoma was reported to have progressed and the patient died six months after surgery [16].

In summary, the relationship between a Y-chromosome gene and gonadal tumor formation in XY gonadal dysgenesis needs to be further investigated. A prophylactic bilateral salpingo-gonadenectomy is necessary for those patients with SRY abnormalities.

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Address reprint requests to:
XIN LU, M.D.
Obstetrics and Gynecology
Hospital at Fudan University
No. 419 Fang-Xie Road
Shanghai, 200011 (P. R. China)
e-mail: xinlu98@yahoo.com