Case Report

A Case Report of 46 XY Partial Gonadal Dysgenesis with Dual Gonadal Tumours

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Abstract

46XY gonadal dysgenesis is known as a disorder of sex development (DSD) that occurs due to abnormality in gonadal development. There is a conflict between one's genotype, phenotype, and gonadal development, which influences the wide range of presentation and clinical appearance of 46XY females. This was a case of a 46XY female who presented with primary amenorrhea with delayed puberty at the age of 18 years old. She had ambiguous genitalia. Her breast and pubic hair were at Tanner Stage 2. Transabdominal ultrasound found a small uterus with a vagina; however, the gonads were not seen. A magnetic resonance imaging (MRI) showed a 20mm right gonad located extra-pelvis near the right iliac vessels while the 9mm streak left gonad was at the usual location next to the sigmoid colon. All her tumour markers were normal except lactate dehydrogenase (LDH) was elevated. She was given estrogen therapy for pubertal induction and underwent laparoscopy prophylactic bilateral gonadectomy. The intraoperative findings were similar to the MRI findings, and the histopathology examination (HPE) results showed left gonadoblastoma and right dysgerminoma FIGO stage 1A. She continued taking estrogen therapy until she had withdrawal bleeding, and oral progesterone was added. 46XY-DSD has high risk of developing germ cell tumour and requires prophylactic gonadectomy as soon as the diagnosis is established. However, delay in presentation and surgery may affect the outcomes and prognosis.

Keywords: Disorders of sex development; dysgerminoma; gonadal dysgenesis; gonadectomy; gonadoblastoma

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Introduction

The disruptions in the complex pathway of sexual differentiation cause disorders of sex development (DSD). Sexual differentiation involves a series of pathways that lead to the differentiation of gonads into testicular tissue and the production of androgen and their actions on the genital tissue (1). The incidence of DSD in live births is estimated to be between 1 in 4500 and 1 in 5000 (2). DSD can be divided into three main categories, which are 46XX-DSD, 46XY-DSD, and sex chromosome DSD.

XY gonadal dysgenesis is one example of 46XY-DSD, and they will have a female phenotype even though they have male chromosomes genetically. Gene mutations can cause this condition during testicular differentiation, including SRY mutations responsible for 10-15% of cases (3). We were presenting a case of 46XY-DSD, which was noted to have a bilateral

gonadal tumour after a laparoscopic gonadectomy was done.

Case Report

A female of 46XY chromosome, who was brought up as a girl, presented to an outpatient clinic in Johor at the age of 18 years old with primary amenorrhea and delayed puberty. There was genital ambiguity, which was not known during her birth. The karyotyping revealed that she was an XY female. Therefore, she was referred to Paediatrics and Adolescents Gynaecology (PAG) unit in Kuala Lumpur for further management. Upon assessment, she wore a hijab and had a female appearance with an average height of 151 cm. Pubic hair and breast were at Tanner stage 2. There was no mass palpable either at the abdomen or inguinal regions. The perineal examination found genital ambiguity with clitoromegaly and hyperpigmented labia majora. She had a normal vaginal canal. Other systemic examinations were unremarkable.

Her hormonal investigations revealed hypergonadotropic hypogonadism with high serum luteinizing hormone (LH) and follicular stimulating hormone (FSH), which were 29.1 mIU/mL and 106 mIU/mL respectively, and low serum oestradiol levels (40 pmol/L). Her serum testosterone level was at the normal range for the female range (0.5 nmol/L). Her thyroid function test and prolactin level were in the normal range. Her cytogenetic study showed 46, XY.

Transabdominal ultrasound found a small uterus with a vagina; however, the gonads were not seen. A magnetic resonance imaging (MRI) of the abdomen and pelvis was done, which reported a small uterus measuring 2.5 x 4.5 cm with a normal vaginal length and features. The right gonad, measuring 20 mm, was located at extra-pelvis and higher up, almost at the pelvic brim, which was anterolateral to the right iliac vessels. There was a streak left gonad with the size of 9 mm at the usual location next to the sigmoid colon. The tumour markers were at normal range except for lactate dehydrogenase (LDH), which was raised: CA125 11 units/mL, BHCG <2.0 IU/L, AFP <2.0 ng/mL, LDH 332 U/L. Following the findings of an enlarged gonad from MRI with elevated LDH, a radio-conference discussion was conducted for pre-operative planning.

Diagnosis of 46 XY partial gonadal dysgenesis and highly suspicious of right gonadoblastoma was made. Counselling and a decision for prophylactic gonadectomy were made between the PAG team and the patient party. However, due to financial restrictions and limited surgery theatre availabilities due to the hospital policies during the COVID-19 pandemic, the surgery was rescheduled several times and only done two years later. She was started on estrogen therapy for pubertal induction. While waiting for the surgery, she was monitored with six monthly transabdominal ultrasounds in our clinic, and the findings were similar to her initial visit.

She eventually underwent an examination under anaesthesia (EUA) with a laparoscopy bilateral gonadectomy. The intraoperative findings showed a 2cm phallus and the labia majora was hyperpigmented with rugae. The vaginal canal was in normal length and appearance, and her cervix was small. The right gonad, 2 x 3 cm in size, was located near the right iliac vessels, and the left gonad was small, measuring 1 x 1 cm (Fig. 1). The uterus was underdeveloped, and both her fallopian tubes were present (Fig. 2). A bilateral gonadectomy was done, and she was discharged home one day after surgery with oral analgesia.

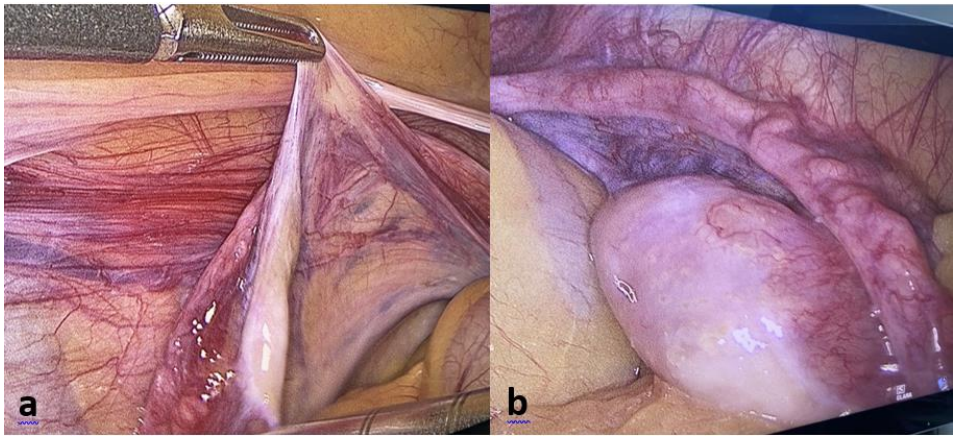

FIGURE 1: (a) Small left gonad; 1(b) Enlarged right gonad.

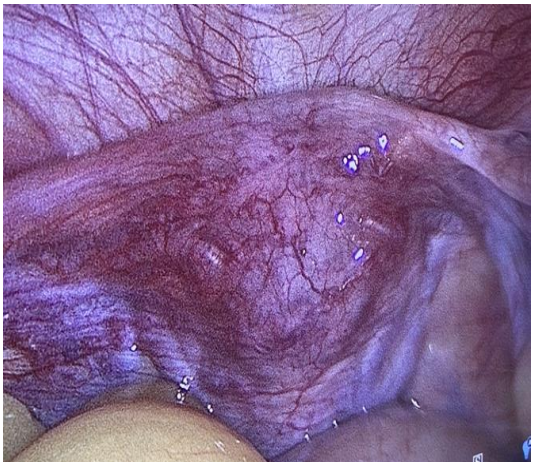

FIGURE 2: Small underdeveloped uterus

The histopathology examination (HPE) result was reported as left gonadoblastoma and right dysgerminoma FIGO stage 1A. Her case was discussed with the gynae-oncology team, and fortunately, she did not require chemotherapy. A positron emission tomography (PET) scan was arranged for her to look for any evidence of metastasis. She was counselled regarding the outcome of the surgery, HPE result, and further surveillance.
She continued taking estrogen therapy after the surgery and successfully had withdrawal bleeding. Subsequently, progesterone pills were supplemented for 14 days every cycle.

Discussion

Partial gonadal dysgenesis (PGD) is one of the rare 46XY-DSD disorders. It is characterised by sex ambiguity involving testicular dysgenesis and ambiguous genitalia and may associated with regression of Müllerian structures (4). The degree of ambiguity ranges from an almost female phenotype with clitoromegaly to an almost male phenotype with isolated hypospadias. Testicular regression syndrome is also considered part of 46XY PGD. PGD is a heterogenous disorder associated with the partial absence of Leydig and Sertoli cell function and deletions or point mutations in the SRY gene. One study reported that a mutation within the high mobility group (HMG) box of the SRY gene helped to maintain the SRY protein's partial function in PGD (5).

The main differential diagnosis of PGD is mixed gonadal dysgenesis (MGD). Patients with PGD and MGD will have the same gonadal and external genitalia characteristics. MGD is usually characterised by a streak gonad on one side with a dysgenetic testis contralaterally. In MGD, they have a 45X cell line with a normal or abnormal Y, the presence of Müllerian structures, and variable degrees of masculinisation. They can be presented as ambiguous genitalia at birth. They may have clinical presentations of Turner syndrome like short stature, limb deformity, thyroid dysfunction, and other malformations, namely cardiac and renal. The presence of clitoromegaly with intact Mullerian structures and without any Turner syndrome features in our patient suggested PGD was more likely.

Patients with PGD have a 25% risk developing germ cell tumours due to dysgenetic gonads with the Y chromosome (6). Gonadoblastoma is the most common tumour and has a 50-60% potential to have a malignant transformation. Unfortunately, for this patient, she had left gonadoblastoma and right dysgerminoma. It is reported that the coexistence of dysgerminoma and gonadoblastoma are seen in about 50% of complete gonadal dysgenesis (CGD) cases (7). However, none has reported in PGD yet. Most dysgerminoma cases are at Stage 1 during diagnosis, and complete resection is adequate. Similarly, this patient was not indicated for adjuvant chemotherapy after surgery.

Due to the significant high risk of germ cell tumour (GCT) in 46XY-DSD individuals with female phenotype compared to the general population, currently, it is recommended to do prophylactic bilateral gonadectomy to prevent the development of gonadal tumour. The estimated prevalence of GCT is 0.8 to 40%, depending on the underlying disorder and age. From the literature, CGD carries the highest risk among all DSDs with 23.3-66.7%, while mosaic turner syndrome with Y chromosome, mixed gonadal dysgenesis, and androgen synthesis/action disorder had relatively low risk (10-16.6%) (7).

A registry-based cohort study found that the age of gonadectomy increased with increasing age at presentation (8). The underlying diagnosis influenced the duration between the presentation age and gonadectomy. The commonest indication is the mitigation of tumour risk, which is known to be low. Some may delay gonadectomy to adulthood, needing meticulous surveillance, which includes 6-monthly gonadal imaging by ultrasound or MRI, tumour markers, and hormonal evaluation. Gonadoblastoma has an excellent prognosis and rarely metastasises, and if it progresses to dysgerminoma, it has low metastatic potential (10).

Post-surgical management in PGD will depend on the HPE diagnosis. Assigned as female, our patient was

given estrogen and progestin to maintain female sexual characteristics as well as bone profile and psychosexual health. She also required regular tumour marker monitoring. In general, it is essential to establish gender identity, corrects the external genitalia based on the chosen gender, minimises the risk of malignancy, preserves fertility chances, and maintains a satisfactory sexual relationship.

Conclusion

PGD is an infrequent condition; however, the dysgenetic gonads in PGD carry a high risk of developing germ cell tumours. Bilateral gonadectomy soon after diagnosis is recommended to ensure a good prognosis.

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