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Case Report

Gonadoblastoma with Dysgerminoma in a Virilized Adolescent with Karyotype 46,XX: A Case Report and Review of the Literature

Kandemir T et al. Virilization in a 46, XX Adolescent

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What is already known on this topic?

Gonadoblastomas typically affect individuals with 46,XY gonadal dysgenesis or females with Y chromosome material, rarely occurring in 46,XX women. Preventive gonadectomy is recommended for those with partial or complete gonadal dysgenesis due to the high malignancy risk associated with the Y chromosome.

What this study adds?

The case enhances knowledge on gonadoblastoma by detailing its presentation, diagnosis, and management. For progressive hirsutism and virilization without typical symptoms like abdominal pain, diagnostic laparoscopy and biopsy may be considered when conventional methods are inconclusive. Confirming the absence of Y chromosomal material is crucial when gonadal dysgenesis is suspected.

Abstract

Gonadoblastoma is a rare ovarian tumor composed of sex cord cells and primitive germ cells. While the majority of gonadoblastomas are found in individuals with 46,XY gonadal dysgenesis, they are also rarely seen in patients with a 46,XX karyotype. We report a case of a fourteen-year-and-six-month-old girl presenting with an uncommon cause of virilization due to a virilizing ovarian tumor. The patient underwent bilateral salpingo-oophorectomy. Upon histopathological examination, the excised tumor was confirmed to be bilateral gonadoblastoma, with dysgerminoma on the left side. Malignant gonadal tumors should be considered in cases of primary gonadal insufficiency with a 46,XX karyotype and progressive virilization. Even when laboratory and imaging tests show no abnormalities, a gonadal biopsy should be considered.

Keywords: Dysgerminoma, gonadoblastoma, XX gonadal dysgenesis, virilization

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Introduction

Hyperandrogenism and the resulting manifestations in young female children can stem from various inherited and acquired causes. In some cases, androgen-producing tumors in the ovaries or adrenal glands can quickly lead to virilization symptoms. Gonadoblastomas are uncommon ovarian tumors composed of sex cord and primitive germ cell components. While gonadoblastomas are typically benign, they are often found alongside invasive germ cell malignancies. Typically, the tumor is observed in individuals with certain gonadal gene mutation syndromes, such as pure or mixed gonadal dysgenesis. The majority of gonadoblastomas are found in individuals with 46,XY gonadal dysgenesis, as well as in females carrying Y chromosome material. However, it is exceptionally rare for gonadoblastoma to occur in women with a normal 46,XX karyotype [1,2]. Due to its exceptionally rare occurrence, we present a case study of a 14.5-year-old girl with a normal karyotype who was diagnosed with gonadoblastoma accompanied by dysgerminoma. We describe the clinical symptoms exhibited by the patient and the outcome of her treatment, along with a comprehensive analysis of previously reported cases of gonadoblastoma occurring in individuals with a typical 46,XX karyotype.

Case Report

A 14.5-year-old girl was referred to our outpatient clinic with a complaint of significant hirsutism over the last 2 months. She was born at term, appropriate for gestational age, to first-degree consanguineous parents after an uneventful pregnancy, and her developmental milestones were normal. Puberty began at the age of 10.5 years, but menarche has not yet occurred. At presentation, her weight, height, and body mass index (BMI) were 42.7 kg (-1.95 SDS), 158.1 cm (-0.5 SDS), and 17.08 kg/m² (1.85 SDS), respectively. The pubertal stage was Tanner 4, and her external genitalia were significant for marked clitoromegaly, measuring 1.5 × 1 cm, with symmetrical labioscrotal folds and no palpable gonads. The modified Ferriman-Gallwey (mFG) score was 16, and a significant deepening of her voice was notable. Otherwise, the systemic examination was normal. Hormonal evaluation revealed high serum luteinizing hormone (LH) (43.4 mIU/L) and follicle-stimulating hormone (FSH) (87.6 mIU/L) levels, confirming the diagnosis of hypergonadotropic hypogonadism. Additionally, serum total testosterone concentration was elevated (1.07 ng/mL). Basal levels of androgen precursors were normal (as shown in Table 1), and adrenal-derived hyperandrogenism was ruled out with a normal response to the corticotropin stimulation test. Tumor markers, including β -human chorionic gonadotropin (β -hCG), α -fetoprotein (AFP), and lactate dehydrogenase (LDH), were normal. Abdominal ultrasound (US) showed no abnormalities, and bilateral adrenal glands were normal. Pelvic US showed that the size of the uterus and ovaries were appropriate for the pubertal stage. In this hypergonadotropic hypogonadism patient with hyperandrogenism, cytogenetic analysis revealed a normal female karyotype (46,XX). Nevertheless, the patient missed follow-up visits for two years. At the age of 16.3 years, she was re-evaluated. During the past two years, she had become increasingly uncomfortable due to progressive hirsutism and needed laser hair removal session every two weeks on her whole body. At this time, the mFG score was 22, and clitoral length was measured at 3 cm. Fibrotic ovarian tissue was detected; however, no abdominal or gonadal mass was visualised on US. Abdominal Magnetic Resonance Imaging (MRI) revealed similar findings (as shown in Table 1). Fluorescence in situ Hybridization (FISH) analysis showed no alterations in the SRY gene. Polymerase chain reaction (PCR) analysis for the SRY gene sequence in the DNA sample obtained from ovarian tissue did not show the presence of SRY. In addition, whole exome sequencing (WES) was performed to comprehensively assess all known genetic disorders, with a particular focus on sex-determining genes such as *WT1*, *SOX9*, and *DAX1*. A laparoscopic gonad biopsy was performed, revealing bilateral gonadoblastoma and unilateral (left) dysgerminoma. Ultimately, the patient underwent bilateral oophorectomy. Pathological examination of the salpingo-oophorectomy material revealed the following macroscopic findings: the right ovary measured 3 × 1 × 0.5 cm, while the left ovary was slightly larger, measuring 2.7 × 1.5 × 3 cm. Microscopic analysis provided further insight into the cellular composition. The specimen revealed the presence of primitive germ cells alongside sex cord stromal cells, all surrounded by ovarian-type stroma. Notably, morphological analysis identified a dysgerminoma in the left ovary. This tumor exhibited characteristic cell cords, featuring both clear and eosinophilic cytoplasm, and measured approximately 0.5 cm in diameter. Immunohistochemical staining was performed to further classify the cellular components. The sex cord cells within the gonadoblastoma stained positively for inhibin, confirming their identity. In contrast, the germ cells within the dysgerminoma stained positively for C-kit, which is a known marker for germ cell tumors. These staining patterns facilitated the differentiation of the various cell types present within the tumor (as shown in Fig.1). No pathological F-18 fluorodeoxyglucose (FDG) uptake was detected on Positron Emission Tomography (PET)/Computed Tomography (CT), and she did not receive any chemotherapy. The bone mineral density Z-score was -1.7, and hormone replacement therapy was commenced following gonadectomy. Pelvic MRI and tumor markers were checked at 6-month intervals, with no abnormal finding was detected.

Discussion

We describe a girl with a 46,XX karyotype who exhibited virilization, a condition rarely caused by gonadoblastoma. The diagnosis of virilization in this girl was clinically challenging due to the variety of potential causes. Various inherited and acquired conditions can contribute to virilization, including disorders of sex development (DSD), virilizing ovarian tumors, adrenal tumors, and exposure to exogenous androgens. Among the DSD conditions, different forms of congenital adrenal hyperplasia (CAH), ovotesticular DSD, and aromatase deficiency can manifest with hyperandrogenic features in females. These conditions contribute to the clinical spectrum of causes that need to be considered when evaluating virilization in a young girl. The severity of virilization served as a crucial clinical indicator, suggesting an ovarian cause as the underlying factor in this girl.

Gonadoblastoma was first recognized as a distinct entity by Scully in 1953. Histologically, it is characterized by the presence of distinct clusters consisting of germ cells and sex cord elements that resemble immature Sertoli or granulosa cells [1]. Histopathologically, our case exhibited sex cord cells in the gonadoblastoma and germ cells in dysgerminoma.

Gonadoblastoma has a high incidence in patients with various syndromes of gonadal maldevelopment that are characterized by the presence of the Y chromosome [2]. Gonadoblastomas are observed in approximately 25% to 30% of patients with XY gonadal dysgenesis and in approximately 15% to 20% of individuals with a karyotype of 45,X/46,XY [2]. However, a significant number of cases have been reported in females with a normal 46,XX karyotype. Pratt-Thomas et al [3] reported a case where unilateral gonadoblastoma was found in association with a ruptured ectopic tubal pregnancy, and the cytogenetic evaluation of peripheral leukocytes revealed a karyotype of 46,XX/45,XO [3].

In individuals with a 46,XX karyotype, the mechanism underlying the development of gonadoblastoma in the absence of a Y chromosome remains unclear. However, potential contributing factors may include somatic mutations, epigenetic changes, or hormonal influences. Somatic mutations in genes like *WT1* and *SF1* may disrupt gonadal development, leading to tumorigenesis. Epigenetic alterations, such as DNA methylation or histone modifications, may silence or activate genes inappropriately, leading to abnormal gonadal development [4,5]. Hormonal influences, such as elevated gonadotropin levels, are thought to potentially play a role in the development of gonadoblastoma; however, the precise mechanisms underlying this association have yet to be fully elucidated [6]. Future studies are essential to elucidate these alternative pathways, and understanding such mechanisms may reveal novel targets for early detection and treatment in 46,XX individuals.

While gonadoblastomas are typically considered benign, they often coexist with invasive germ cell malignant tumors. The most prevalent malignancy found in association with gonadoblastomas is pure dysgerminoma. However, other variants, such as immature teratoma, embryonal carcinoma, yolk sac tumor, and choriocarcinoma, can also be observed. In Scully's review of 74 gonadoblastoma cases, it was found that approximately 50% of the tumors were accompanied by dysgerminoma as a coexisting germ cell tumor. This is similar to our case and consistent with previous studies. Other types of germ cell tumors, such as embryonal carcinoma, yolk sac tumor, and teratoma, were also reported in a few cases [1,7].

In our review of the literature since 1990, we identified 14 cases of gonadoblastoma in females with a normal 46,XX karyotype [7-20]. Table 2 presents a summary of the clinical characteristics observed in these 14 cases as documented in the literature. While abdominal symptoms, such as abdominal pain or the presence of a mass, were the most common complaints in the 15 reported cases (66%, 10/15 cases), it is important to note that cases can also present with symptoms such as vaginal bleeding, menstrual disorders, and virilization. Our case stands out from the other reported cases due to several distinctive findings. Firstly, there was an absence of abdominal pain, which is a common complaint in similar cases. Additionally, both physical examination and imaging tests (ultrasound and MRI) did not reveal the presence of any masses. Furthermore, the levels of tumor markers such as AFP, β -hCG, and LDH were not significantly elevated. Given these unique characteristics, the most crucial aspect of our case was the diagnosis made through diagnostic laparoscopy.

These distinguishing features set our case apart from others reported in the literature. In the case reported by Chandrapattan Pet et al. [19], similar to our case, the chief complaint was virilization. Furthermore, contrasexual pubertal development was observed in that particular case.

In individuals with partial or complete gonadal dysgenesis, preventive bilateral gonadectomy is commonly recommended due to the increased risk of gonadal malignancy (15% to 50%) associated with the presence of the Y chromosome [20]. It is crucial to confirm the absence of Y chromosomal material. Typically, peripheral blood lymphocyte karyotyping is performed to detect Y chromosomes in the germline; however, there is a possibility of missing small chromosomal fragments containing Y chromosome material. In our case, PCR analysis for the SRY gene sequence in the DNA sample obtained from the ovarian tissue did not demonstrate the presence of SRY.

Surgery is the primary treatment method for the management of gonadoblastomas. The specific surgical approach may vary depending on the extent and characteristics of the tumor. It is important to consider individual patient factors and provide appropriate adjunct therapies, such as chemotherapy, to support the overall treatment plan. Out of the 14 cases documented in the literature, chemotherapy was administered in nine cases. Due to the localized and small nature of the tumor in our patient, chemotherapy was deemed unnecessary.

Conclusion

To conclude, this case prompts us to reconsider the notion that gonadoblastoma only occurs in abnormal gonads. As additional cases are reported, more comprehensive evidence regarding the prevalence of gonadoblastomas in functionally and morphologically normal gonads may emerge, providing further clarification on this matter. Furthermore, it is crucial to consider that when managing hirsutism and progressive virilization, laparoscopy should be performed, and biopsies may provide guidance when imaging methods and laboratory tests fail to yield a definitive diagnosis. Further studies are needed to elucidate the etiopathogenesis of the reported cases.

Statements

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Statement of Ethics

This study was conducted in compliance with the terms of the Helsinki II Declaration and written informed consent was obtained from the parents on behalf of the children. In our country, this type of clinical study does not require Institutional Review Board/Institutional Ethics Committee approval to publish the results.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

T.K. and E.K.O. collected patient information. A.A. performed molecular analysis. O.D. performed the surgery. A.B. and S.O. performed the pathological evaluation. All authors were involved in preparing the manuscript. All authors approved the final manuscript for submission and agree to be accountable for all aspects.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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Figure 1. The figure illustrates the histopathological appearance of the biopsy specimens. A: Area of gonadoblastoma with calcification. Hematoxylin and eosin, x40 magnification. B: An area of dysgerminoma consisting of germ cells. Hematoxylin and eosin, x100 magnification. C: Staining of sex cord cells in gonadoblastoma with inhibin. x20 magnification. D: Staining of germ cells in the area of dysgerminoma with C-kit. x40 magnification.

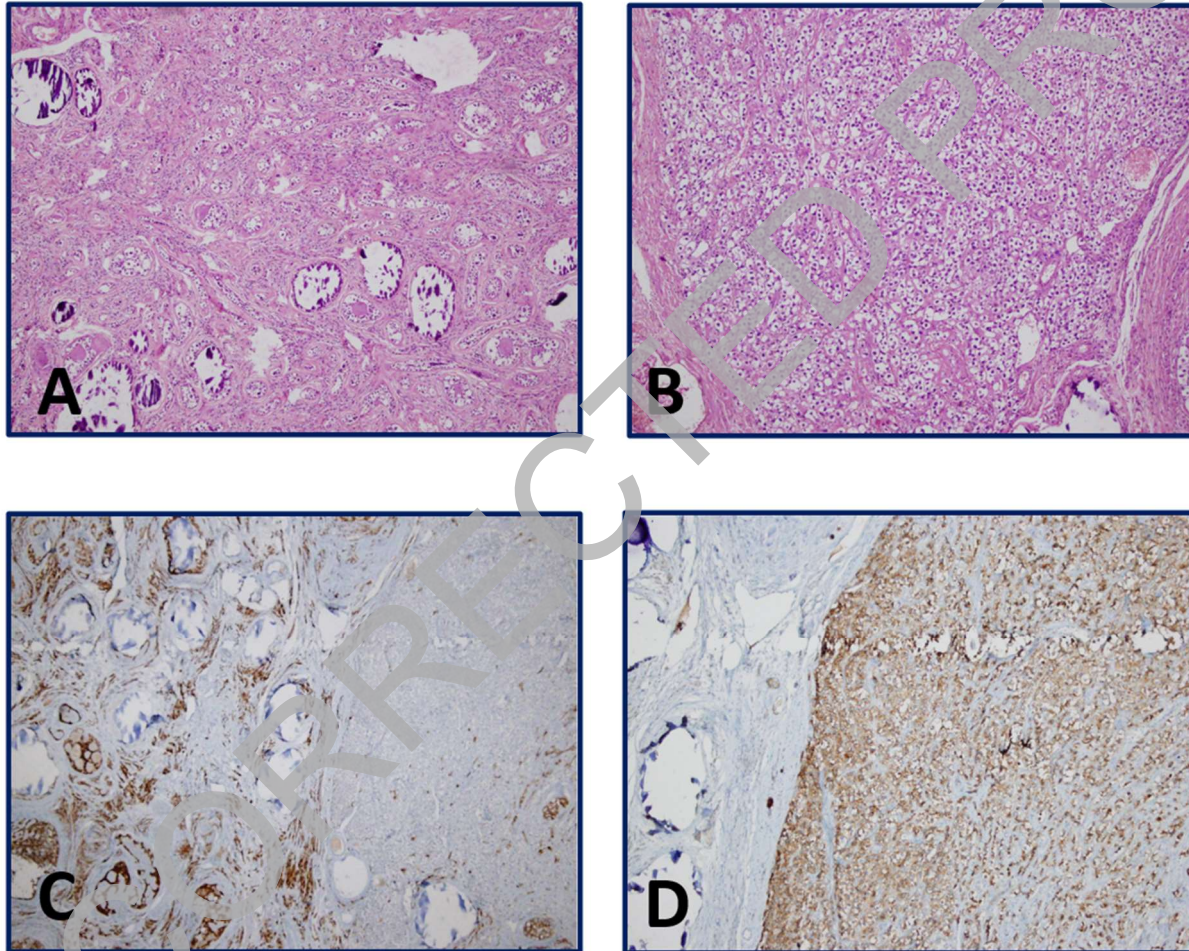


Table 1: Clinical, laboratory and radiological examination of the patient during follow up

	At initial time	Before gonadectomy	After gonadectomy
Age (years)	14.6	16.3	17.2
Anthropometric evaluation			
Height, cm (SDS)	158.1 (-0.5)	159.5 (-0.51)	159.5(-0.6)
Weight, kg (SDS)	42.7 (-1.95)	42.4 (-2.47)	40.6 (-3.0)
BMI, kg/m ² (SDS)	17.08 (-1.85)	16.6 (-2.72)	15.9 (-3.7)
Puberty Tanner Clitoromegaly	B4/4 P5 2-1.5 cm	B4/4 P5 3 cm	B5/5 P5 2.5x2cm
Ferriman-Gallwey score	16	22	NA
Hormonal findings			
LH, mIU/mL (N: 0.4-11.7)	43.4	32	43.7
FSH, mIU/mL (N: 1-9.2)	87.6	85	86.6
E ₂ , pg/mL (N: 12.5-166)	26.7	20	32
T, ng/mL (N: 0.23-1.39)	1.07	1.57	0.07
DHT, pg/mL (N: 30-180)	114	NA	NA
T/DHT	9.3	NA	NA
AMH, ng/mL (N:0.62-7.8)	3.05	3	NA
DHEA-S, ug/dL (N: 44-248)	331	317	NA
Cortisol, ug/dL (N: 8-19)	18.2	NA	NA
ACTH, pg/mL (N: 6-48)	19	17	NA
17-OHP, ng/mL (N:0.44-2.35)	0.57	NA	0.8
1,4 AS, ng/mL (N:0.5-2.24)	1	4.1	1.6
AS/T (N: >0.8)	0.93	2.6	22.9
P, ng/ml (N: 0.057-0.893)	0.37	NA	NA
SHBG, nmol/L (N: 36-125)	NA	24.7	NA
CA 19.9, U/mL (N:0-34)	NA	NA	13.6
β-hCG, mIU/mL (N:<5)	0.93	NA	NA
AFP, ng/ml (N:<13.6)	2.2	1.9	1.8
LDH, U/L (N:150-300)	166	223	170

Imaging			
Pelvic US	Uterus: 41x17x65 mm Right adnexa: 9.5 ml Left adnexa: 10.9 ml	Uterus: 28x13.3x63 mm cervix/fundus:1 Adnexa: Bilateral ovaries could not be clearly distinguished. Isoechoic tissue areas containing cystic openings, which may be compatible with the follicle cyst, whose volume was measured as 1.1 ml on the right and 1 ml on the left, were observed in the ovarian lobes. Fibrotic ovarian tissue?	
Pelvic MRI		Uterus: uterine size, parenchyma and echogenicity are normal Ovaries: could not be seen	Uterus: 43x18x11 mm, its dimensions are reduced. Ovaries: Bilateral ovaries were not seen.
Histopathology			
		Bilateral gonadoblastoma and unilateral (left) dysgerminoma	
<p><i>ACTH: Adrenocorticotrophic hormone, AFP: α-fetoprotein, AMH: Anti-Mullerian Hormone, BMI: Body mass index, CA 19-9: Carbohydrate antigen 19-9, 1,4 AS: 1,4 Androstenedione, DHEA-S: Dehydroepiandrosterone sulfate, DHT: Dihydrotestosterone, E2: Estradiole, FSH: Follicle-stimulating hormone, β-hCG: Human chorionic gonadotrophin, LDH: Lactate dehydrogenase, LH: Luteinizing hormone, 17-OHP: 17-Hydroxy Progesterone, N: Normal value, NA: Not available, P: Progesterone, SHBG: Sex hormone binding globuline, T: Total testosterone, US: Ultrasonography, MRI: Magnetic Resonance Imaging</i></p>			

Table 2: A review of published female cases of gonadoblastoma with karyotype 46, XX

No	Author	Year	Age at diagnosis	Clinical presentation	Fertile status	Hormonal abnormalities	Laterality	Karyotype	Tumor size	Surgical procedure	Pathological findings in addition to gonadoblastoma	Adjuvant therapy
1	Erhan Y et al [8]	1992	26	Abdominal mass during pregnancy	Fertile	NR	Right	46, XX	20 cm	TAH + BSO	Dysgerminoma	Chemotherapy
2	Obata NH et al [7]	1995	10	Abdominal discomfort	No	NR	Bilateral	46, XX	8 cm	USO + right Ovarian cystectomy	Left with dysgerminoma, right with dysgerminoma and yolk sac tumor	Chemotherapy
3	Zhao S et al [9]	2000	27	Abdominal pain	Fertile	NR	Right	46, XX	10x8x 6 cm	USO + chemotherapy + later TAH + USO + LND + omentectomy	Choriocarcinoma, embryonal carcinoma, yolk sac tumor, immature teratoma and dysgerminoma	Chemotherapy
4	Erdemoglu E et Al [12]	2007	19	Abdominal mass and pain	No	NR	Unilateral	46, XX	25x22x20 cm	USO	Endodermal sinus tumor	None
5	Yilmaz B et al [10]	2010	20	Abdominal mass	No	NR	Bilateral	46, XX	21x21x11 cm	BSO	Bilateral with dysgerminoma	Radiation and chemotherapy
6	Koo YJ et al [11]	2011	34	Vaginal bleeding	Fertile	NR	Left	46, XX	12 x9x 7 cm	USO + paraaortic LND	Dysgerminoma	Chemotherapy
7	Esin S et al [13]	2011	15	Vaginal bleeding	No	NR	Left	46, XX	0.5 cm	USO	Dysgerminoma	None
8	Kanagal DV et al [14]	2013	14	Abdominal distension	No	Elevated testosterone level	Left	46, XX	30x25x10cm	USO + pelvic and para-aortic LND + infracolic omentectomy	Dysgerminoma	Chemotherapy
9	Kulkarni MM et al [15]	2016	20	Abdominal pain	Fertile	NR	Left	46, XX	8x6x6 cm	USO + omental biopsy	Dysgerminoma	None
10	McCuaig JM et al [16]	2017	20	Oligomenorrhea and menorrhagia	No	NR	Left	46, XX	2.5x2x1.5 cm	USO	Dysgerminoma	None

11	Roth LM et al [17]	2019	9	Abdominal pain and a right adnexal mass	No	NR	Right	46, XX	8.9×5.7×5.2 cm	USO	Mixed germ cell tumor	Chemotherapy
12	Raafey MA et al [18]	2020	10	Abdominal pain, abdominal distention and fever	No	NR	Left	46, XX	16x10x9 cm	USO	Dysgerminoma	Chemotherapy
13	Chandrapattan P et al [19]	2022	9	Signs of virilization and contrasexual pubertal development	No	NR	Right	46, XX	15x10 cm	USO + pelvic LND + infracolic omentectomy	Dysgerminoma	Chemotherapy
14	Min Yin et al [20]	2022	11	Abdominal pain	NR	Elevated FSH, LH, progesterone, 11-deoxycortisole, ACTH, corticosterone decreased cortisol, E2, testosterone	Right	46, XX, gonadal karyotype Y chromosome negative	10x8x6 cm	USO	Dysgerminoma	17 β -hydroxylase /17,20-lyase deficiency Glucocorticoid replacement therapy
15	Our case	2024	14.6	Hirsutism	No	Elevated FSH, LH, total testosterone	Bilateral	46, XX SRY negative	3x1x0.5 cm (right) 2.7x1.5x3 cm (left) 0.5 cm (left) dysgerminoma	BSO	Bilateral gonadoblastoma and unilateral (left) dysgerminoma	None

BSO, bilateral salpingo-oophorectomy; USO, unilateral salpingo-oophorectomy; LND, lymph node dissection; TAH, total abdominal hysterectomy; NR, not reported