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Case Report

Dysgerminoma presenting at fifty, consequence to undiagnosed Swyer syndrome

Sapna Vinit Amin¹, Aswathy Kumaran^{2*}

¹Department of Obstetrics and Gynecology, Kasturba Medical College, Manipal, Karnataka, India

²Department of Reproductive Medicine, Aster MIMS, Kottakkal, Kerala, India

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***Correspondence:**

Dr. Aswathy Kumaran,

E-mail: astral17us@gmail.com

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ABSTRACT

Swyer syndrome or XY complete gonadal dysgenesis (CGD) is a rare disorder of sex development (DSD) characterized by presence of dysgenetic gonads in a phenotypically female patient with a male karyotype. Usually Swyer syndrome is diagnosed following appropriate evaluation for amenorrhea in adolescence and prophylactic gonadectomy is done as these patients have high risk of developing malignancy in their dysgenetic gonads. Here we presented patient who presented later in life with gonadal malignancy which turned out to be a consequence of undiagnosed Swyer syndrome. Her case exemplifies that fact that improper evaluation of primary amenorrhea in adolescence and omission to do prophylactic bilateral gonadectomy led to her presenting with malignancy at this advanced age. Therefore, be aware to not let Swyer syndrome go undiagnosed and mismanaged.

Keywords: Reproductive Health, Cancer prevention, Swyer syndrome, Gonadal dysgenesis, Dysgerminoma

INTRODUCTION

The Swyer syndrome is a rare disorder of sex development (DSD), characterized by the failure of the gonads to develop. This was first described Dr. Swyer in 1955.¹ Synonymously 46 XY complete gonadal dysgenesis (CGD) or gonadal dysgenesis, XY female type, the incidence is estimated to be around 1 in every 80,000 births. These women have female phenotype as well as internal and external genitalia but with streak/dysgenetic gonads that render them infertile. They often present with primary amenorrhea. Mutations of genes that are involved in normal sex differentiation of a fetus with an XY (male) karyotype are believed to be causative. The abnormal Y chromosome in dysgenetic gonads tends to induce abnormal in the germ cells resulting in development of benign gonadoblastoma in around 30 percent of women with Swyer syndrome. Often the tumor is the presenting symptom on the evaluation of which the woman is diagnosed with 46 XY CGD. These tumors may become malignant forming a dysgerminoma which unless

managed expeditiously can be life threatening and associated with significant morbidity. Here we presented the case report of a 50-year-old woman with abdomino pelvic mass whose final diagnosis was Swyer syndrome with dysgerminoma the malignant conversion having occurred as a consequence of appropriate diagnosis and management for Swyer syndrome having been missed in adolescence.^{2,3}

CASE REPORT

A 50-year-old female, presented with complaints of lower abdominal pain since 1 month, complaints of loss of weight and burning micturition since 1 month and history of primary amenorrhea at the gynecological outpatient department in our tertiary teaching hospital in South India in 2013. At 18 years of age, she was evaluated for primary amenorrhea and underwent laparoscopy elsewhere (reports not available, she had never been advised gonadectomy). She menstruated normally with cyclical hormonal replacement for 10 years, later she stopped. She

got married at 35 years of age and had no problems in sexual activity. Her family history was negative for ambiguous genitalia and sex reversal.

On examination, patient had female phenotype, weight of 40 kg, height of 165 cm, arm span of 185 cm, with marfanoid habitus (Figure 1). Vertex-pubis- 82 cm, pubis heel- 82 cm, breast tanner stage 2, pubic hair- 3, axillary hair- nil. On examination abdomen was soft, non-tender with palpable abdominopelvic mass of 14 weeks, with no evidence of ascites. On per speculum examination, vagina and cervix were normal to her age. On per vaginal examination a firm mass of 14 cm, mobile, non-tender, separate from the atrophic uterus was felt.

USG abdomen and pelvis done showed small uterus, thin endometrium, large mass with heterogeneous echogenicity with cystic areas, attached to fundus of uterus with band of tissue, mass does not appear to be vascular, ovaries not visualized, no significant free fluid in pouch of douglas. MRI abdomen- large well-defined heterogeneously enhancing solid lesion with areas of necrosis in the pelvis along the midline. Mild ascites. No significant lymphadenopathy, possibility of ovarian malignancy in the left adnexa

Blood investigations revealed an increased level Beta HCG of 7794 mIU/ml, high FSH 73.5 mIU/ml, normal levels of CA 125, LDH, alpha fetoprotein, testosterone level of 35 ng/ml, a normal heamogram, renal and liver function tests. Thus, a preliminary diagnosis of germ cell tumor of the left gonad was reached and the patient was posted for laparotomy with surgical staging.

Laparotomy revealed an infantile uterus and tubes, a large abdomino-pelvic mass from the left gonad (Figure 2) of 10×10 cm with solid and cystic areas. Right gonad appeared as band of tissue (streaky ovary). Minimal ascitic fluid present, and taken for the cytology. Total abdominal

hysterectomy with bilateral salpingo-gonadectomy and omentectomy was done.



Figure 1: Increased arm span- Swyers.



Figure 2: Left gonad replaced by solid tumor.

Table 1: Pathological examination.

Gross examination (Figure 3)	Microscopic examination (Figure 4 and 5)
<p>Uterus with cervix measured 4.5×3×2 cm</p> <p>Endometrium was atrophic, endomyometrium measured 0.8 cm at its thickest cervix was unremarkable.</p> <p>Right adnexal mass measured 2.5×1.5 cm, cut section showed grey white areas. No well-defined ovarian parenchyma.</p> <p>Tube measured 5 cm in length. Left gonadal mass measured 10×8×8 cm. Cut section showed a grey white solid tumor with small foci of hemorrhage Attached tube measured 5 cm in length.</p> <p>Omentum: On cut section, 2 lymph nodes/deposits identified largest measuring 1.3×1 cm. 2 sections.</p>	<p>Endometrium showed glands in proliferative phase. Myometrium-normal. Cervix- normal.</p> <p>Right adnexa showed scant spindle shaped ovarian cortical stromal like cells with rete ovary and thick walled congested hilar vessels suggestive of streak ovary. Tubes showed normal plicae. Sections from omentum showed one tiny reactive lymph node and no tumor deposits seen.</p> <p>Left gonadal mass showed tumor composed of large ovoid malignant cells arranged in dis-cohesive nests and islands with focally well-defined cell border, moderate amount of eosinophilic to clear cytoplasm, large pleomorphic nuclei, some with 1-2 nucleoli along with occasional areas showing interspersed syncytiotrophoblasts and mitosis separated by fibrous septae with diffuse lymphoplasmacytic infiltrate, focal ill-defined histiocytic aggregates, congested vessels, foci of tumor necrosis with adjoining punctate calcification and areas of hemorrhage. Lymphatic tumor emboli seen. No normal ovarian tissue was seen.</p>



Figure 3: Gross specimen of hypo plastic uterus and dysgerminoma.

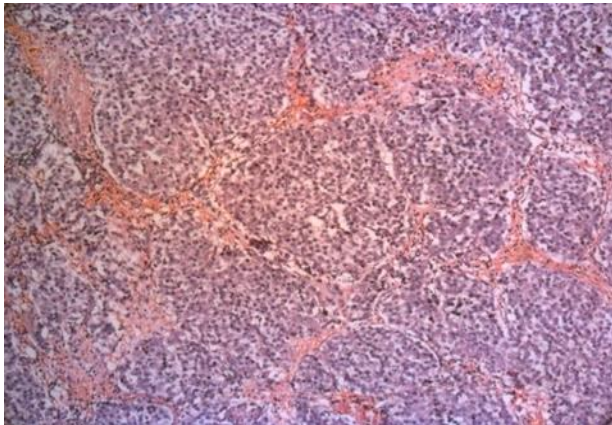


Figure 4: Microscopy of gonadal tumor.

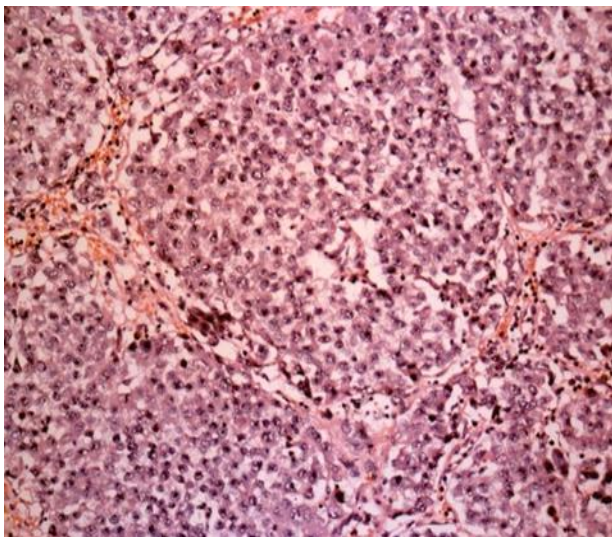


Figure 5: Histopathological Inference of specimen- left sided dysgerminoma with syncytiotrophoblasts, right side streak gonad, normal omentum and reactive lymph node, splenosis.

Her karyotype report was 46 XY. The surgical staging and the histopathology report led to the final diagnosis of

dysgerminoma (germ cell tumor) stage I, grade 1, in fifty years old woman with Swyer syndrome. As there was no evidence, of metastasis/local spread, no adjuvant chemotherapy treatment was advised and she was asked to come for regular three-monthly follow-ups. She has been doing so for one year with no adverse event.

DISCUSSION

Any disturbance in the development of the gonad may result in gonadal dysgenesis. When a chromosomal drive to the gonad is weak, hypoplasia of the gonad is likely. It is the functional Y chromosome in a male fetus that drives the bipotential gonad to develop in to testes. The hormones from the newly formed and functional testes in fetal life, leads to the development of male external and internal genitalia and involution of the precursors of the female genitalia (mullerian duct). The Y chromosome if absent or nonfunctional lead to the development of dysgenetic gonad and female genitalia by default and regression of the Wolffian system. The ovary that is formed is nonfunctional and dysgenetic. Functional ovaries develop from the bipotential gonad only if two normal X chromosomes are present; as in a fetus with an normal female XX karyotype. In XO karyotype (Turner syndrome), again the gonad is dysgenetic.⁴ Short arm Y chromosome deletion involving SRY, a mutation in other genes that leads to inhibition of SRY function or mutation of SRY function are some of the causes attributed to the development of Swyer syndrome.^{4,5}

Our patient was 50 years old and had marfanoid habitus. She had female phenotype with normal uterus and right-side streaky gonad and left gonadal malignant tumor and karyotype 46 XY making her a case of XY complete gonadal dysgenesis (CGD) or Swyer syndrome. The patient first presented with primary amenorrhea at 18 years. Then at 50 years, she presented with pain abdomen and was detected to have an abdominopelvic mass that turned out to be an gonadal dysgerminoma.

Germ cells from the dysgenetic gonads are prone for defective mitosis and meiosis. Karyotyping abnormalities including aneuploidy are common in dysgenetic gonads. Dysgerminoma tend to occur in dygenetic gonads with Y chromosomes, hence a normal female karyotype (or at least a normal phenotype) should be confirmed if the contra lateral gonad has to be preserved in women with complete gonadal dysgenesis.^{3,4} Gonadoblastoma is the more common tumor in patients with gonadal dysgenesis with karyotype 46 XY occurring in around 30%. These are prone for malignant conversion to dysgerminoma due to presence of abnormal Y chromosomes.^{3,4} Dysgerminomas contain syncytiotrophoblast cells as single or small group of cells, which produce HCG. Hence, HCG is the tumor marker for these germ cell tumors. Kawai et al analyzed seven-tumor marker in germ cell tumors of the ovary.⁶ He showed positive rate of CA-125 was over 50% in all germ cell tumor types except mature cystic teratoma. Therefore, CA 125 is useful for all the screening of malignant germ

cell tumor. In our case CA 125 was normal but BHCG high 7760 IU, and LDH was slightly elevated and histopathology showed dysgerminoma.

Behtash et al have published on dysgerminoma that developed in three phenotypically female patients with normal secondary sexual characteristics with 46 XY pure gonadal dysgenesis. All patients had presented with abdominopelvic mass. Laparotomy, gonadectomy done, and postoperative adjuvant chemotherapy had been given.⁷ Radakovic et al found gonadoblastoma and dysgerminoma in 55% of the patients with Swyer syndrome.⁸ Mixture of dysgerminoma and yolk sac tumor is the single most common combination in a mixed primitive germ cell tumor. Most patients with XY gonadal dysgenesis present with delayed pubertal development and primary amenorrhea. Clure et al observed secondary amenorrhea in female with Swyer syndrome associated with a hormonally active tumor.⁹ Thus, hormonally active gonadoblastoma/dysgerminoma producing estrogens resulting in development of secondary sexual features and withdrawal bleeding may mask the presence of gonadal dysgenesis and delay the diagnosis of the pathology.

All women diagnosed within Swyer syndrome should have prophylactic B/L gonadectomy of the dysgenetic gonads to prevent germ cell tumor development. Women with gonadoblastoma, which is benign, again require bilateral gonadectomy along with tumor. Patients presenting with dysgerminoma should promptly be managed with Laparotomy tumor excision gonadectomy and surgical staging. Stage one, grade tumors require only tumor resection gonadectomy and follow ups alone. Advanced dysgerminoma should be managed with, gonadectomy, pelvic and para aortic lymphadenectomy and omentectomy. They should receive 3-6 cycles of Bleomycin, Etoposide, Cisplatin (BEC) chemotherapy and lifelong follow-ups with periodic clinical, radiological and tumour marker evaluation. If the uterus is retained it can be removed in case of evidence of neoplasm or after childbearing is over.

The women presenting early in prepubertal to premenopausal age group should undergo gonadectomy and then be on cyclical estrogen progesterone hormone replacement so that secondary sexual characters and uterus develop, and osteoporosis is prevented. They may opt for Donor oocyte in vitro fertilisation and embryo transfer program for childbearing. Karimian et al have reported a rare case of Swyer syndrome whose uterus remained hypoplastic and unresponsive to hormone replacement even though secondary sexual characters developed suggesting that factors other than estrogen might be responsible for uterine development.¹⁰

CONCLUSION

Swyer syndrome or XY complete gonadal dysgenesis may have various presentations including primary amenorrhea, infertility or with aggressive germ cell tumors.

Karyotyping to rule out presence of dysfunctional Y chromosome should be done in all cases of dysgenetic gonads, as these are the women who tend to develop gonadoblastoma that may undergo malignant conversion to dysgerminoma, unless prophylactic gonadectomy is done. This case report of a woman who had been evaluated in adolescence for primary amenorrhea but presented at age fifty with dysgerminoma, as prophylactic gonadectomy had not been done earlier exemplifies this fact.

Hence, never let Swyer go undiagnosed. Always advice prophylactic gonadectomy when Swyer syndrome is diagnosed and reciprocally all women newly diagnosed with Swyer syndrome should be evaluated to rule out germ cell tumors.

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