CASE REPORT

DOI: 10.5336/jcog.2022-88756

Familial Swyer Syndrome; Complete Pure Gonadal Dysgenesis in Two Sisters, Manifested as Two Different Clinics and Associated with 46 XY-Karyotype

Ozan KARADENİZ[a], Engin ÇELİK[a], Merve KORKMAZ ABUAMER[a], Nermin GÜNDÜZ[b]

[a]Department of Gynecology and Obstetrics, Division of Gynecologic Oncology,
University of Health Sciences Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Türkiye
[b]Department of Pathology, University of Health Sciences Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Türkiye

ABSTRACT Index case - a 19-year-old female patient was admitted with the main complaint of unbearable abdominal pain and additionally having a history of primary amenorrhea. The physical examination and hormonal profile demonstrated hyper-gonadotropic hypogonadism and elevated serum tumor markers. The radiological imaging revealed a massive pelvic mass and hypoplastic uterus. Histopathology of the pelvic mass resulted in a malignant mixt germ cell tumor International Federation of Gynaecology and Obstetrics Stage IIIA. After tumor-free debulking surgery, she was referred to a medical oncology unit where four cycles of chemotherapy were applied with bleomycin, etoposide, and cisplatin. The family history unearths the elder sister at age 20 had similar aspects such as primary amenorrhea and the same physical semblance as her sister. Chromosome karyotype analysis of the 2 sisters revealed 46, XY which led to our diagnosis of Swyer syndrome. The family has been given counseling about their situation and advised for other siblings to be evaluated.

Keywords: Familial Swyer syndrome; mixed germ cell tumor; primary amenorrhea; gonadal dysgenesis; karyotype

46, XY pure gonadal dysgenesis (GD) first described by Swyer as "male pseudohermaphroditism" characterized by a normal female external genitalia, phenotypically normal female with bilateral streak gonads, hypoplastic uterus, normal Müllerian structures, elevated gonadotropins, normal testosterone, and low estrogen levels, lack of development at secondary sexual characteristics with primary amenorrhea.[1] These patients catch up as normal females until the condition emerges first in adolescence with primary amenorrhea and tardy puberty. Besides, those individuals are in jeopardy of developing ovarian cancer as dysgerminoma and gonadoblastoma in particular.[2] For the past few years, familial inheritance has been reported and there were studies about the identification of novel genes in the literature.[3]

CASE REPORT

A 19-year-old female, the youngest child of her family and born to a consanguineous couple, was admitted to our gynecologic oncology outpatient clinic with unbearable pelvic pain. Her anamnesis revealed that she had primary amenorrhea without any problem with her secondary sex characteristics. Besides, her family history showed that the patient's elder sister was admitted to a different gynecology outpatient clinic with primary amenorrhea 6 months earlier.

On physical examination, her weight was 61 kg, height was 170 cm, and body mass index was 21.1. She had normal female-type external genitalia, Tanner Stage III breast development, Tanner Stage IV pubic hair growth, a normal vagina and cervix, and no

Correspondence: Ozan KARADENİZ
Department of Gynecology and Obstetrics, Division of Gynecologic Oncology,
University of Health Sciences Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Türkiye
E-mail: dr.ozankrdnz@gmail.com

Peer review under responsibility of Journal of Clinical Obstetrics & Gynecology.

Received: 06 Feb 2022 ***Received in revised form:*** 09 Aug 2022 ***Accepted:*** 22 Aug 2022 ***Available online:*** 26 Aug 2022

clitoromegaly or any other evidence of virilization. Her abdomen was stiff and there was a mobile palpable mass in the lower part of her abdomen extending to the umbilicus. Preoperative abdominal ultrasonography revealed a large 19×16 cm adnexal mass that expanded through the bilateral lower quadrants of the abdomen, which was hard to determine its origin. Contrast-enhanced magnetic resonance imaging (CE-MRI) at the T2-A series was enlightened that the diameters of the uterus were 5×1.8 cm and confirmed abdominal pelvic mass (17×18×19 cm) which contains calcifications and minimal papillary projections (Figure 1a). For further investigation, hormonal and blood sample analyses were performed (Table 1). Her laboratory test results showed a serum follicle-stimulating hormone (FSH) level of 133 IU/mL and a luteinizing hormone (LH) level of 59.7 IU/mL which were both in the post-menopausal range. Tumor marker levels were as follows; elevated lactate dehydrogenase level of 638 U/L (135-214 U/L), high alpha-fetoprotein level of 1210 ng/mL (<=7), and increased serum human chorionic gonadotropin level of 5696 (<5.3).

Considering the elevated levels of serum tumor markers and the size of the pelvic mass, the possibility of an underlying malignancy was higher, therefore the patient underwent laparotomy with a frozen section for exploration. The abdominal observation revealed a torsioned massive 20 cm ovarian mass with cystic and hemorrhagic areas originating from the left adnexa (Figure 1b). The uterus was hypoplastic and bicornuate shaped (Figure 1c). Bilateral fallopian tubes were infantile. The right ovary was streak and infantile (Figure 1d). Left salpingo-oophorectomy was performed and the intraoperative frozen section reported a high-grade malignant ovary tumor. The patient subsequently underwent pelvic and para-aortic lymphadenectomy,

TABLE 1: Serum and hormonal analysis of two sisters with Swyer syndrome.

Parameter	Index case	Elder sister	Normal range
FSH (mIU/mL)	133	134	Follicular phase: 3.5-12.5 Ovulatory phase: 4.7-21.5 Luteal phase: 1.7-7.7 Post-menopausal: 25.8-134.8
LH (mIU/mL)	59.7	59.9	Luteal: 1.0-11.4 Follicular: 2.4-12.6 Post-menopausal: 7.7-58.5 Ovulation: 14.0-95.6
E_2 (pq/mL)	9	8	Follicular phase: 12.5-166 Ovulatory phase: 88.5-400 Luteal phase: 43.8-211 Post-menopausal: <5-10 Pregnancy: 215-400
TSH (µIU/mL)	2.2	2.45	0.27-4.2
Testosterone (ng/mL)	0.38	0.3	0.06-0.82
DHEA (µg/dL)	265	230	148-417
Beta-hCG (mIU/mL)	5696	1.1	<5.3
LDH (U/L)	638	175	135-214
Alpha-fetoprotein (ng/mL)	1210	1.72	<=7
CA-125 (U/mL)	142	6	<35
CA-19-9 (U/mL)	5.6	9.01	<27
CA-15-3 (U/mL)	14.9	9.5	<=25
CEA (ng/mL)	<0.3	<0.3	non-smokers <3.8 smokers <5.5

FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; TSH: Thyroid-stimulating hormone; DHEA: Dehydroepiandrosterone; hCG: Human chorionic gonadotropin; LDH: Lactate dehydrogenase; CA: Cancer antigen; CEA: Carcinoembryonic antigen.

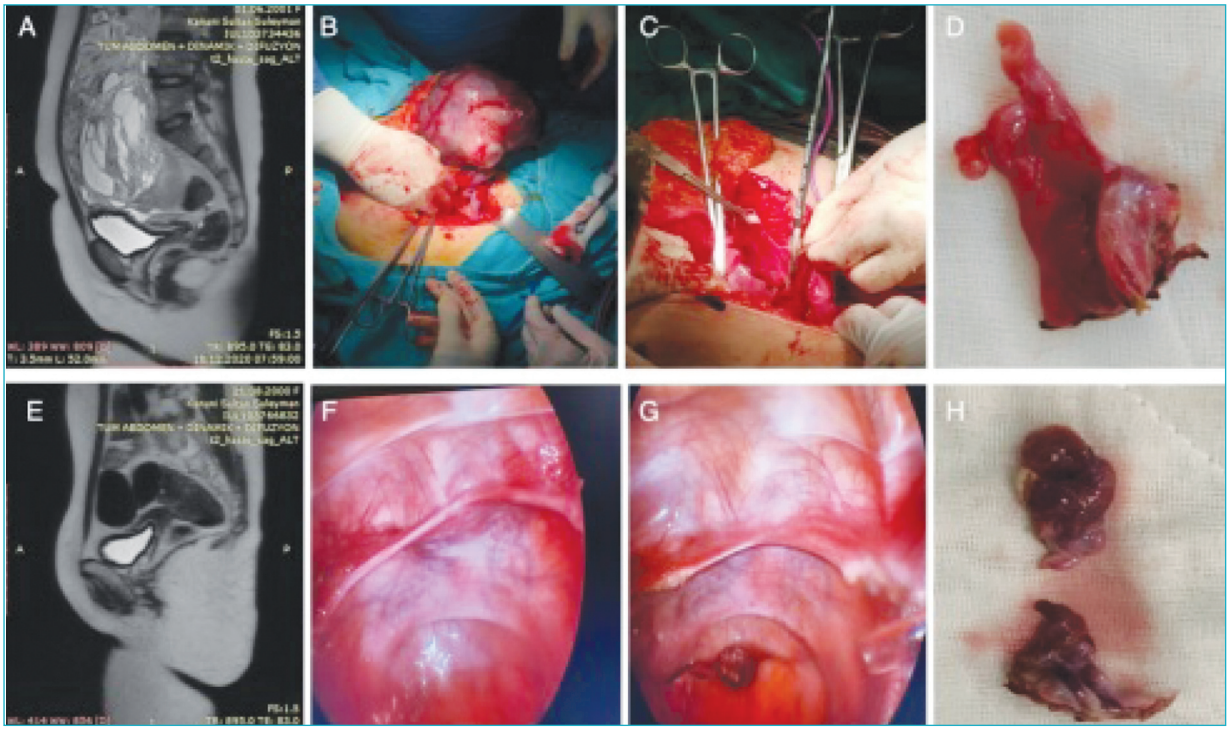

FIGURE 1: CE-MRI findings and laparotomic observation of adnexal mass and uterus of the index case, CE-MRI findings and laparoscopic observation with gonadectomy of the elder sister. **A)** CE-MRI at the T2-A series showing infantile uterus and abdominal pelvic mass (17×18×19 cm) which contain calcifications and minimal papillary projections of the index case; **B)** Torsioned massive 20 cm ovarian mass with cystic and hemorrhagic areas originated from the left adnexa of the index case; **C)** Hypoplastic and bicornuate shaped uterus of the index case; **D)** Streak and infantile right ovary of the index case; **E)** CE-MRI at the T2-A series showing hypoplastic uterus without any adnexal mass of the elder sister; **F)** Laparoscopic image of the hypoplastic uterus of the elder sister; **G)** Laparoscopic image of gonadectomy of the elder sister; **H)** Bilateral streak and infantile gonadectomy and salpingectomy of the elder sister. CE-MRI: Contrast-enhanced magnetic resonance imaging.

resection of great omentum, and right salpingo-oophorectomy. Postoperative hematoxylin and eosin stained paraffin histopathology resulted in a mixed germ cell tumor comprised of dysgerminoma having thin stroma surrounded by islets of cells accompanied with lymphocytic infiltration, yolk sac tumor having cystic formations of different sizes, the embryonal carcinoma part consists of cells with papillary and glandular structure, with large nuclei and prominent nucleoli in the left ovary (Figure 2a, Figure 2b, Figure 2c). Immunohistochemical staining results showed CD117 (+), placental alkaline phosphatase (+) at the dysgerminoma component, alpha-fetoprotein (+), glypican 3 (+) at the yolk sac component, and CD30 (+) at the embryonal carcinoma component. Microscopic para-aortic lymph nodal mass involvement with a size of 15 mm lymph node and 4 mm metastatic focus, conversely no involvement at bilateral obturator and pelvic lymph node was reported. Final histopathology resulted in International Federation of Gynaecology and Obstetrics Stage III-A. The chromosomal analysis of the patient exposed 46, XY karyotype (Figure 2d).

The elder sister who called for further assessments visited our outpatient clinic. On her physical examination, the patient is tall and thin with a height of 172 cm and a weight of 58 kg. She had normal female-type external genitalia, Tanner Stage II breast development, Tanner Stage II pubic hair growth, a normal vagina and cervix, and no clitoromegaly or any other evidence of virilization like her younger sister. Her hormonal profile results indicate as follows; serum FSH level 134 mIU/mL, serum LH level 59.9 mIU/mL, and E2 8 pg/mL. Serum tumor marker results were unremarkable. Her hormonal profile suggested primary gonadal failure and cytogenetic analysis revealed 46, XY pure GD. CE-MRI at the T2-A series of the abdomen showed a hypoplastic uterus

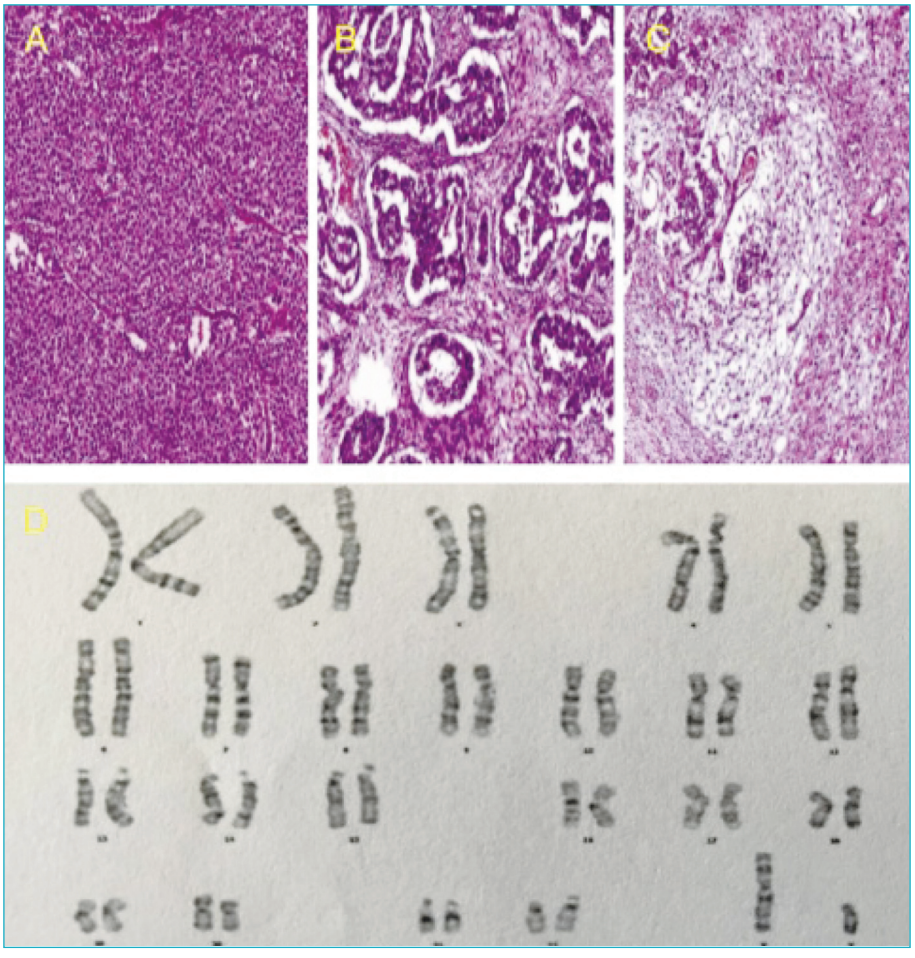

FIGURE 2: Histopathology of left ovary and karyotype analysis of the index case. A) Dysgerminoma. H and E staining, original magnification ×100; B) Embryonal carcinoma tumor. H and E staining, original magnification ×100; C) Yolk sac tumor. H and E staining, original magnification ×100; D) Chromosomal analysis of the case 1 showing 46, XY karyotype.

with a size of 2x1.2 cm and no evidence of adnexal mass (Figure 1e). Laparoscopic bilateral gonadectomy and salpingectomy were scheduled for the patient because of the risk of gonadoblastoma development. Laparoscopic observation showed a hypoplastic uterus with bilateral streak gonads (Figure 1f). Bilateral salpingo-oophorectomy was performed and the sample was sent to pathology (Figure 1h). The pathology resulted in the ovarian stroma, rete testis, Leydig cell hyperplasia, and atrophic seminiferous tubules at the right ovary.

For both sisters, the chromosome analysis resulted in XY karyotype, which then oriented us to the cytogenetic analysis of the *SRY* gene. *SRY* gene analysis revealed a genetic microdeletion. The patient has been given counseling about her situation and referred to the nearest psychology department for psychological evaluation. Additionally, we advised our patient to get her remaining siblings evaluated. The patient and her elder sister provided written informed consent for their information and images to be published.

DISCUSSION

46, XY pure GD or Swyer syndrome is an extremely rare entity that consists of a genetically heterogeneous group of disorders that resulted from a failure of early-stage differentiation at gonadal development. According to gene involvement, Swyer syndrome can be inherited as autosomal dominant (NR5A1 mutations, heterozygotic mutations DHH, WNT4 duplications), autosomal recessive (homozy-

gotic or heterozygotic DHH mutations), X-linked (NROB1, STARD8), or Y-linked (SRY mutations). Mutations in the short arm of the Y chromosome with the involvement of the *SRY* gene or other genes that affect SRY function consist of approximately 15%-20% of those individuals.[4] The remaining majority of the individuals (80-90%) are H-Y negative and sporadic. In the literature, a few familial cases of Swyer syndrome have been reported.[5,6]

While evaluating differential diagnosis of Swyer syndrome, the practitioners must rule out and consider the possibility of 45, X/46, XY mosaicism because of the increased risk for cardiovascular anomalies associated with 45, X cell line (Turner syndrome).[7] Swyer syndrome in early puberty is crucial on account of the high risk for developing gonadoblastoma. Prophylactic gonadectomy is recommended following the diagnosis of Swyer syndrome. A rigorously taken anamnesis approach with suspicion and evaluation from hormonal, clinical, radiological, and genetic aspects is needed to unearth the familial Swyer syndrome.[8] The treatment of this condition requires multidisciplinary teamwork with a comprehensive plan for providing care for the patient's ongoing life. Hormone replacement therapy should be given for preventing bone loss and osteoporosis, promoting the development of secondary sexual characteristics, and inducing the expansion of the uterus convenient for pregnancy. A few cases of Swyer syndrome associated with pregnancy have been reported in the literature which has demonstrated that although those patients have an undeveloped uterus, the assistance of artificial reproductive techniques provided normal pregnancies.[9,10] Meanwhile surrogacy and adoption are alternative ways of having children for those patients.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Engin Çelik, Ozan Karadeniz;* ***Design:*** *Ozan Karadeniz;* ***Control/Supervision:*** *Ozan Karadeniz, Engin Çelik;* ***Data Collection and/or Processing:*** *Ozan Karadeniz, Nermin Gündüz;* ***Analysis and/or Interpretation:*** *Ozan Karadeniz, Merve Korkmaz Abuamer;* ***Literature Review:*** *Merve Korkmaz Abuamer;* ***Writing the Article:*** *Ozan Karadeniz;* ***Critical Review:*** *Ozan Karadeniz, Engin Çelik;* ***References and Fundings:*** *Nermin Gündüz;* ***Materials:*** *Ozan Karadeniz.*

REFERENCES

1. Swyer GI. Male pseudohermaphroditism: a hitherto undescribed form. Br Med J. 1955;2(4941):709-12. [Crossref] [PubMed] [PMC]
2. Radaković B, Jukić S, Buković D, Ljubojević N, Cima I. Morphology of gonads in pure XY gonadal dysgenesis. Coll Antropol. 1999;23(1):203-11. [PubMed]
3. Ilaslan E, Calvel P, Nowak D, Szarras-Czapnik M, Slowikowska-Hilczer J, Spik A, et al. A case of two sisters suffering from 46,XY gonadal dysgenesis and carrying a mutation of a novel candidate sex-determining gene STARD8 on the X chromosome. Sex Dev. 2018;12(4):191-5. [Crossref] [PubMed]
4. Uehara S, Hashiyada M, Sato K, Nata M, Funato T, Okamura K. Complete XY gonadal dysgenesis and aspects of the SRYgenotype and gonadal tumor formation. J Hum Genet. 2002;47(6):279-84. [Crossref] [PubMed]
5. Ates S, Batmaz G, Sevket O, Molla T, Dane B. Familial Swyer syndrome in two sisters with undeveloped uterus. J Obstet Gynaecol. 2014;34(6):540-1. [Crossref] [PubMed]
6. Bagci G, Bisgin A, Karauzum SB, Trak B, Luleci G. Complete gonadal dysgenesis 46,XY (Swyer syndrome) in two sisters and their mother's maternal aunt with a female phenotype. Fertil Steril. 2011;95(5):1786.e1-3. [Crossref] [PubMed]
7. Chand MT, Turner S, Solomon LA, Jay A, Rabah R, Misra VK. A case of 45,X/46,XY mosaicism presenting as Swyer syndrome. J Pediatr Adolesc Gynecol. 2020;33(5):577-80. [Crossref] [PubMed]
8. Dimitri P, Cohen M, Wright N. Indications for familial screening and gonadectomy in patients with 46,XY gonadal dysgenesis. Int J Gynaecol Obstet. 2006;95(2):167-8. [Crossref] [PubMed]
9. Creatsas G, Deligeoroglou E, Tsimaris P, Pantos K, Kreatsa M. Successful pregnancy in a Swyer syndrome patient with preexisting hypertension. Fertil Steril. 2011;96(2):e83-5. [Crossref] [PubMed]
10. Shah JS, Viteri OA, Longo M, Abdallah M, Sibai B. Twin gestation in a Swyer syndrome patient with superimposed pre-eclampsia. J Obstet Gynaecol. 2018;38(5):719-20. [Crossref] [PubMed]