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Dysgerminoma in a Patient with 46, XY Karyotype and Pure Gonadal Dysgenesis (Swyer Syndrome): A Case Report and Literature Review

Short title: Dysgerminoma in a Patient with 46, XY Karyotype

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Abstract

Disorders of sex development (DSD) result from intrauterine defects in sex discrimination. The clinical phenotype differs based on the disease type. Cases with ambiguous external genitalia are diagnosed at birth. However, diagnosis of cases with normal-appearing external genitalia may be delayed until puberty. Here, we report a patient with a pelvic mass and a small uterus that was diagnosed by abdominal ultrasound, in addition to the history of primary amenorrhea and physical examination suggested Swyer syndrome, confirmed by genetic karyotyping. Pathological examination of the surgically removed mass revealed dysgerminoma. Until the age of 19, the patient did not have any idea about 46, XY karyotype, and assumed to be a female. The development of dysgerminoma (as a result of the simultaneous presence of gonadal dysgenesis and Y-chromosome) was another challenge that the patient had to deal with. The diagnosis of this patient at an earlier age could have prevented the development of gonadoblastoma, by removal of the streak gonads. By the presentation of this case, we intend to increase the physician's awareness about DSDs; earlier diagnosis may help the patient deal with her disease better and reduce the risk of further complications.

Keywords: Disorders of sex development, Disorders of sex development 46, XY, Gonadal dysgenesis, 46, XY, Karyotype

Introduction

"Is it a boy or a girl?" This is the first question everyone asks after the birth of a child. The discrepancy between the genetic sex and the phenotypic sex is an increasingly frequent finding, with an incidence of 1 in 1,500-2,000 pregnancies (1). Intrauterine impairment in the arrangement of the unipotential gonad into binary pathways results in disorders of sex development (DSD) that causes atypical internal and/or external genitalia (2). Individuals with DSD suffer from several social and psychological problems and their treatment is complex (3). Some cases are hard to diagnose, as they have distinctive external genitalia and mild symptoms; 46, XY DSD is one such case.

Incomplete intrauterine masculinization results either from the decreased synthesis of testosterone or from the impaired activity of androgen; the dysgenetic abdominal gonads fail to secrete anti-müllerian hormone (AMH) and testosterone, resulting in 46, XY DSD. These patients may present with several phenotypes, ranging from atypical or female external genitalia with male gonads identified in most; but in some, no gonadal tissue is found (4). These patients generally seek medical attention at pubertal age, because of the absence of breast development and/or amenorrhea (5); however, delayed diagnosis is observed in patients with complete female phenotype or very mild undervirilization, entitled complete gonadal dysgenesis (CGD) or Swyer syndrome (6).

Patients with gonadal dysgenesis and Y-chromosome material are at a high risk of developing gonadoblastoma with the potential for malignant transformation to dysgerminoma, estimated to occur in 37-45% of patients with 46, XY DSD (6-8).

Here, we present a 19-year-old female patient who was not aware of the presence of DSD and was referred for an abdominal ultrasound, which revealed a pelvic mass, in addition to the history of primary amenorrhea and physical examination suggested Swyer syndrome. Karyotyping revealed 46, XY in the patient. During surgery, the mass was removed and sent to pathology, which revealed dysgerminoma,

Case Report

In late September 2022, a 19-year-old female was referred to our center (Omid Hospital, Mashhad, Iran) with a history of primary amenorrhea; she had menstruation only twice with medication. It

was about more than a year that she had no menstruation, at the time of referral. Family history revealed a positive history of menstrual disorders in cousins.

She had no complaint of abdominal pain or gastrointestinal disorder. In physical examination, she had a palpabale mass in pelvic, small breasts, and scattered hair in the pubis and axilla. External genitalia were female phenotype. Her weight was 85 kg and her height was 175 cm (body mass index = 27.8 kg/m^2).

A venous blood sample was taken from the patient, analysis of which revealed a normal serum level of fasting blood sugar (FBS; 102 mg/dL), normal urea (19 mg/dL), creatinine level (0.9 mg/dL), and thyroid stimulating hormone (TSH; 1.9 mμ/L), normal prolactin (484 MIU/L), and follicle-stimulating hormone (FSH; 99.4 IU/L), normal level of cancer antigen 19-9 (CA 19-9; 14.5 U/mL), CA 125 (12.5 U/mL), alpha-fetoprotein (AFP; 2.9 ng/mL), increased level of luteinizing hormone (LH; 35.9 IU/L) and carcinoembryonic antigen (CEA; 5.1 ng/mL).

During the abdominal ultrasound from the uterus and adnexa, performed by a radiology specialist, a small-sized uterus for age (27 × 50 mm) was revealed with a homogenous echo of the myometer, and endometrial line of 2.7 mm. In addition, it revealed a solid cystic heterogenic lesion (60 × 85 × 95 mm), completely vascular, in the midline pelvis with a pushing effect on the uterus fundus and bladder, suggestive of a tumoral lesion of the pelvis. Adnexa could not be visualized or separated from the lesion. Based on these results, history of primary amenorrhea, physical examination results, and small uterus in ultrasound, Swyer syndrome was suspected for the patient. Therefore, the karyotyping examination was requested, which revealed 46, XY (male chromosome) that reversed her sex (male pseudohermaphrodism) and confirmed the diagnosis of Swyer syndrome. Twenty GTG-banded metaphases were investigated from the culture of PHA-stimulated peripheral blood in two flasks at a resolution of 450-550 BPH (Figure 1).

Based on these results, the patient was scheduled for surgery. Left salpingo-oophorectomy was first performed for the patient and sent as a frozen for pathological examination. The macroscopic evaluation revealed a 9 × 7 × 2 cm ovary with a solid creamy tan cut surface and a 6 × 0.5 cm tube. Observation of the nests of large uniform epithelioid cells separated by fibrous septa containing lymphocytes in microscopic examination of the frozen sectioning of the left ovary suggested the diagnosis of dysgerminoma. Therefore, according to the karyotype of the patient the surgeon decided to remove the atrophic ovary on the other side, omentum, pelvic and para-aortic lymph

nodes; all of which were sent to the laboratory for pathological examination. Ascites was not observed during surgery, and the patient's uterus was preserved for future pregnancies.

Permanent sections of the left ovary, submitted in 12 blocks, revealed nests of large uniform polygonal cells with clear to eosinophilic cytoplasm and distinct cell membranes with many mitoses separated by fibrous septa containing lymphocytes and many non-caseating granulomas, composed of epithelioid histiocytes and multinucleated giant cells with focal calcification without the involvement of ovarian surface and fallopian tube, that confirm frozen section diagnosis of dysgerminoma (Figure 2). Lymphovascular and perineural invasion was seen. The results of the immunohistological examination showed nuclear positive for OCT3/4 and SALL4, membranous and cytoplasmic positive for PLAP, and negative for CD30 and AFP (Figure 3).

Omentum, right ovary, and tube were tumor-free. The total number of pelvic and para-aortic lymph nodes found was one 2.5-cm lymph node that was also involved by dysgerminoma, with a 1.2 × 0.5 cm tumor deposit; no extranodal extension was observed. The tumor was classified as FIGO stage of III A1 (ii), based on the latest version of the protocol of College of American Pathologists (9).

After the surgery, the patient received four chemotherapy cycles, including bleomycin, etoposide, and cisplatinum (BEP); at the time of writing this case report (4 months follow-up), the patient was in good condition.

Discussion

Here, we reported a case with a late diagnosis of female sex reversal syndrome (Swyer syndrome); this patient had normal female external genitalia, and amenorrhea was her only gynecology-related problem. The late diagnosis of this syndrome resulted in the development of dysgerminoma in the patient, which complicated the patients' condition. Therefore, reporting this case is of great value, as it calls attention to the early evaluation of females with primary amenorrhea and considering Swyer syndrome and chromosomal anomalies in differential diagnosis, in order to prevent the formation of malignant gonadal tumors by removal of the gonads. In the following, we discuss different aspects of this rare syndrome.

Clinical manifestation and diagnosis

Cases with ambiguous genitalia are easy to diagnose; not only by the physician, but also by the parents and anyone who sees the infant's genitalia. However, many patients with different DSDs have normal-appearing genitalia, presenting a phenotype of female or male external genitalia; while the genotypic sex of the individual is not consistent with this phenotype. Patients with Swyer syndrome also have female genitalia and normal Müllerian structures, resulting from the complete absence of virilization or undervirilization (10). Furthermore, gonads are atrophic without hormonal potential, which makes diagnosis more challenging (11). Some patients have a normal uterus (as in our case) and can become pregnant, using hormone therapy and/or assisted reproduction techniques (12, 13). This is why some patients remain undiagnosed during their whole lifetime unless karyotyping is performed; the current recommendation is to refer any female with amenorrhea until the age of 14 (11).

It is about a century since Swyer introduced two cases of male pseudohermaphrodism with female external genitalia and complete gonadal dysgenesis; since then (1955), this syndrome was named after Swyer. Still, this syndrome is very rare (1:30.000 and 1:80.000 live births); 90% of cases present in adolescence with a median time to diagnosis of 1.5 years (11). However, there are reports of late diagnosis, even in newly published case reports (published in 2022-2023, diagnosed at the age of 23 (14), 26 (15) and 25 year-old females (16)). Furthermore, some presentations are reported as atypical in case reports, while they should have been suspected as Swyer syndrome earlier (17).

Genetics

Evidence has suggested the role of SRY mutations in Swyer syndrome, a candidate gene for testis determining factor on the Y chromosome. SRY is also responsible for the activation of SOX9 transcription, a crucial gene in the determination of sex, and its mutations can result in partial or gonadal dysgenesis in such patients. Other mutations in sex-determining pathways have also been suggested (11). These genetic studies are confirmed by the clinical presentation of Swyer syndrome in families (18) and sisters (13, 19), suggesting familial Swyer syndrome. Taking the family history of our patient also showed menstrual disorders in the cousins of the patient, who might have had the same disease. However, none were diagnosed with Swyer syndrome. Familial

screening of karyotype may be the key to diagnosis, although familial involvement is observed infrequently (in about 4%) (11, 19).

Paraclinical study

Serological evaluation (measurement of LH, FSH, TSH, sex hormone binding globulin, estradiol, testosterone, and anti-müllerian hormone) is suggested, in addition to tumor markers, in cases with gonadal dysgenesis. The patient presented here also underwent a serological examination, which revealed increased levels of LH and CEA. Unfortunately, in our patients, the late diagnosis resulted in dysgerminoma. Because of the tumor and free fluid in the abdominal ultrasound, ovaries could not be visualized; but the uterus appeared normal (with a smaller size). An abnormal uterus may be the key to diagnosis in patients who undergo imaging of the abdomen; however, streak gonads (resulting from lack of AMH) usually result in normal uterus development, like in our case, which complicated diagnosis.

In addition to Swyer syndrome, it is also important to pay attention to the possible simultaneous presence of other rare syndromes or diseases, associated with it, which may co-occur due to the missense sequence variation; such as cutaneous disorder (ulerythema ophryogenes), caused by a missense sequence variation in MAP3K1 (20). Some may also have simultaneous malignancies, beside gonadal tumor; such as the case presented with acute lymphoblastic leukemia simultaneous with gonadal mixed germ tumor (21). Furthermore, patients with childhood malignancies may be additionally missed as chemotherapy-induced premature ovarian insufficiency (22). Therefore, it is important to consider this syndrome in any female patient, referring with primary amenorrhea with absent/insufficient signs and symptoms of secondary sexual development.

Treatment

After diagnosis, treatment is necessary. The main treatment of DSD is the removal of gonads, because their presence can result in development of malignancy, specifically gonadoblastoma and dysgerminoma, in the dysgenetic gonads with typically para-aortic lymph node metastasis (23). Considering the scant literature available, the exact risk of developing malignancy is not clear and some have reported no malignancy even in cases diagnosed late (at the age of 25) (16); therefore, gonadectomy is suggested in every patient with diagnosis of this syndrome. Gonadectomy is suggested, even after development of malignancy (15).

Another important aspect in patients with DSD is the choice of sex, especially in cases with late diagnosis. These patients have lived as females for several years and neither the patient nor the family was aware of the presence of DSD until this age. The news of the diagnosis of this sex reversal syndrome, itself, is a challenging issue for the patient and the family; therefore, a psychological consult is a necessary stage of treatment. In addition to estrogen therapy, patients with problems with genitalia require genital surgery; but the outcomes of surgery in uncertain, although evidence suggests performing this surgery. In a study on 57 individuals in Germany, about half were dissatisfied with the results of surgery and clitorial arousal (47%), 37.5% with overall sex life, and most had problems with desire (70%), arousal (53%), and dyspareunia (56.3%) (24).

Malignancy

Gonadoblastoma results from the transformation of the germ cells in the dysgenetic gonads and is observed almost exclusively in individuals with DSDs who have a Y chromosome or testis-specific protein Y-encoded 1, such as syndrome of gonadal dysgenesis, androgen insensitivity syndrome, or Turner's syndrome; most cases of gonadoblastoma are non-invasive or in situ (25). While, dysgerminoma (that arises from the primordial germ cells), the commonest lesion in these individuals is a very malignant tumor that rapidly infiltrates the adjacent organs, with distant metastasis and frequent recurrences. Similarly, our patient was diagnosed with a large dysgerminoma with lymphovascular and perineural invasion; FIGO stage of III A1[ii] with metastasis to para-aortic lymph node >1 cm. Surgery and chemotherapy are the main treatments suggested for dysgerminoma; however, the prognosis is poor, especially in advanced stages.

Several cases of dysgerminoma are reported in patients with Swyer syndrome at different ages and at different stages (26-29). Apparently, the risk of developing this neoplasm increases with age, estimated at about 5% until the age of 15, increasing to 27.5% at the age of 30, considering the longer exposure to germ cells. The high risk of developing dysgerminoma and the invasive nature of this malignancy is why bilateral gonadectomy with salpingectomy is essential as a prophylactic treatment in these patients (30). Co-occurrence of tumors, such as dysgerminoma and gonadoblastoma (31, 32), dysgerminoma and choriocarcinoma (33), or dysgerminoma and yolk sac tumor (34), have been also reported, which suggests the high risk of malignancy in these patients and emphasizes on the need for prophylactic removal of gonads that requires an early

diagnosis of Swyer syndrome. Therefore, it is necessary that physicians pay greater attention to patients with the chief complaint of primary amenorrhea and consider the presence of DSDs, especially rare cases with normal phenotypes, like 46, XY syndrome, for appropriate treatment, preventing the development of malignancies in the patient.

The rarity of this syndrome may be the cause of missed diagnosis in many cases. Therefore, it is important that the physicians be aware of the early symptoms of this rare syndrome and perform complete physical examination and history taking for patients with primary amenorrhea and absent secondary sexual development, in order to diagnose this syndrome early and appropriately, before malignancy develops. It has to be considered that the news of Swyer syndrome is shocking for the patient and similar to several DSDs, it is hard for the patient and the family to accept the presence of this disease. Reports of refusal for gonadectomy in patients diagnosed with Swyer syndrome show the necessity of educating physicians for breaking this bad news to the individual and the family members, in order to reduce or eliminate the risk of refusal for the necessary prophylactic treatment that can prevent the development of dysgerminoma in the patient (35). Furthermore, screening the other girls in the family (sisters and female cousins) can be an important step for early diagnosis.

Conclusion

Here, we reported a case who developed dysgerminoma as a result of a late diagnosis of Swyer syndrome. Considering the few cases reported in the literature, reporting the characteristics of each new case can help increase the knowledge about clinical course, diagnosis, and treatment strategies. As discussed here, patients with Swyer syndrome may have normal female external genitalia; therefore, the patient may be missed to be diagnosed as a DSD. Most refer to physicians with primary amenorrhea. Therefore, physicians should pay greater attention to these cases and consider the possibility of having DSD in these patients. Besides the problems in menstruation, sexual life, and pregnancy, the dysgenetic gonad predisposes the patient to dysgerminoma, gonadoblastoma, or other malignancies, which have a poor prognosis. Early diagnosis of Swyer syndrome and early removal of the gonads can prevent the development of these malignancies and save the patient from the risk of this malignancy.

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Figures

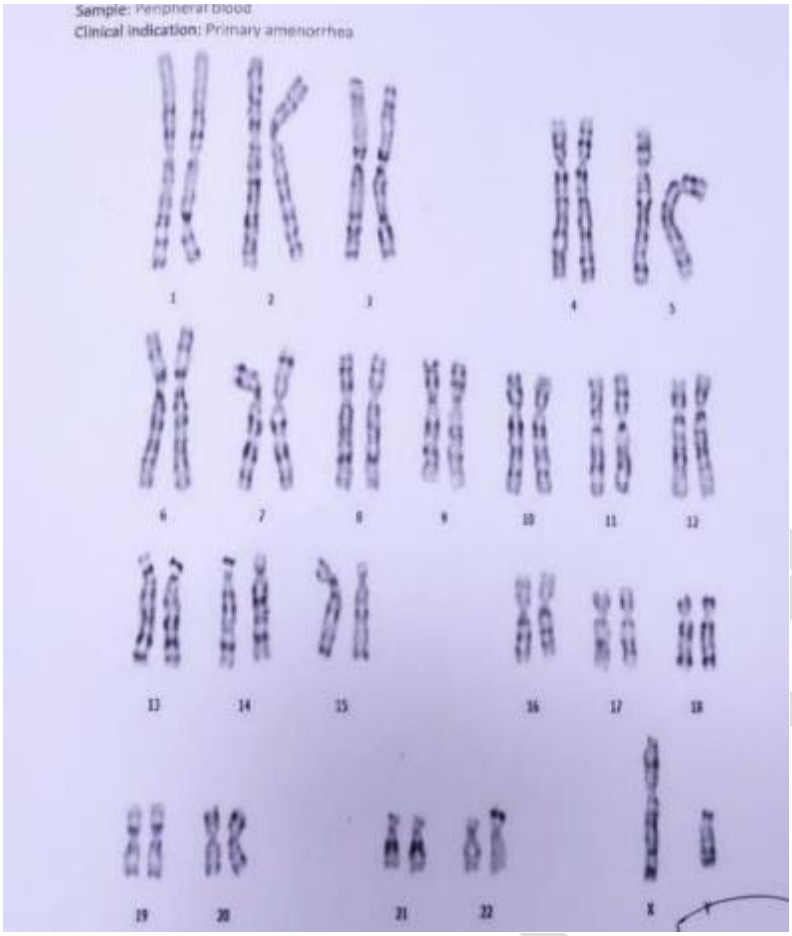

Figure 1. Karyotype figure

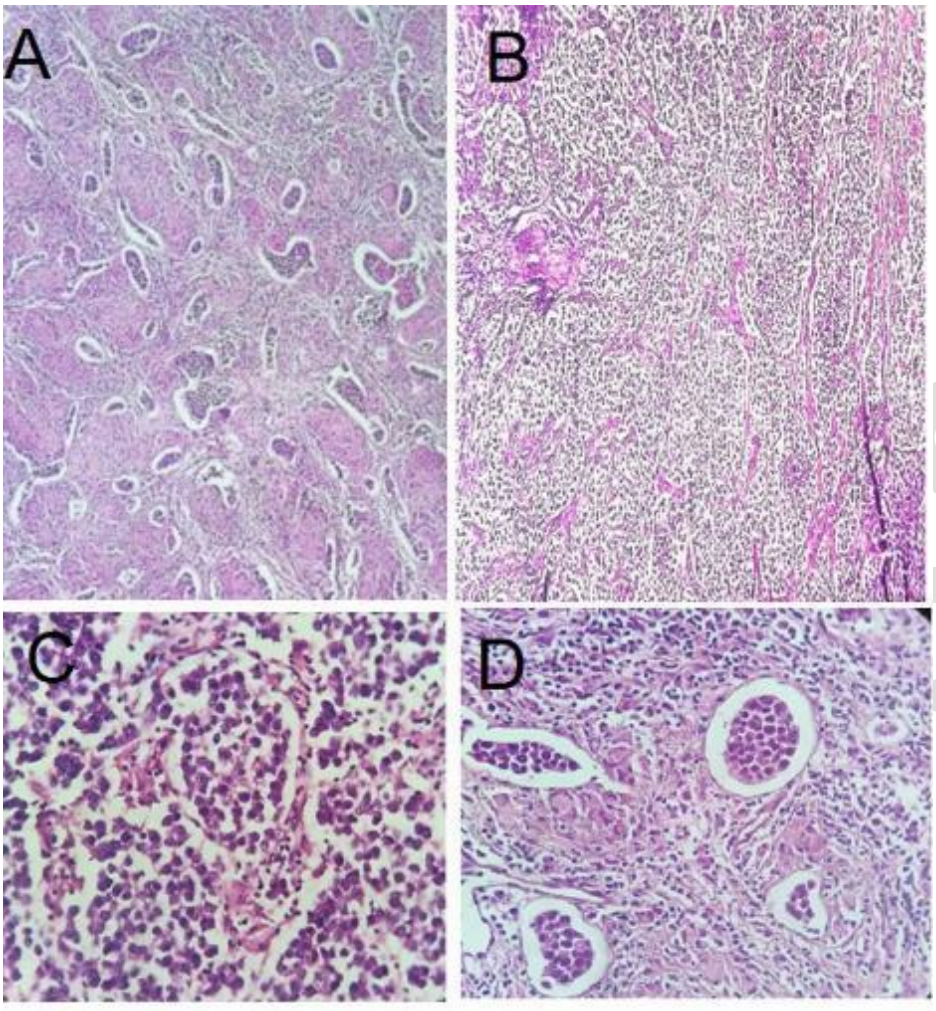

Figure 2. Microscopic evaluation of ovary, revealing nests of uniform polygonal cells with distinct cell membranes, clear to eosinophilic cytoplasm, and prominent nucleoli separated by fibrous septa containing lymphocytes and many non-caseating granulomas. Stained with hematoxylin and eosin and magnification of 100 (A and B) and 400 (C and D)

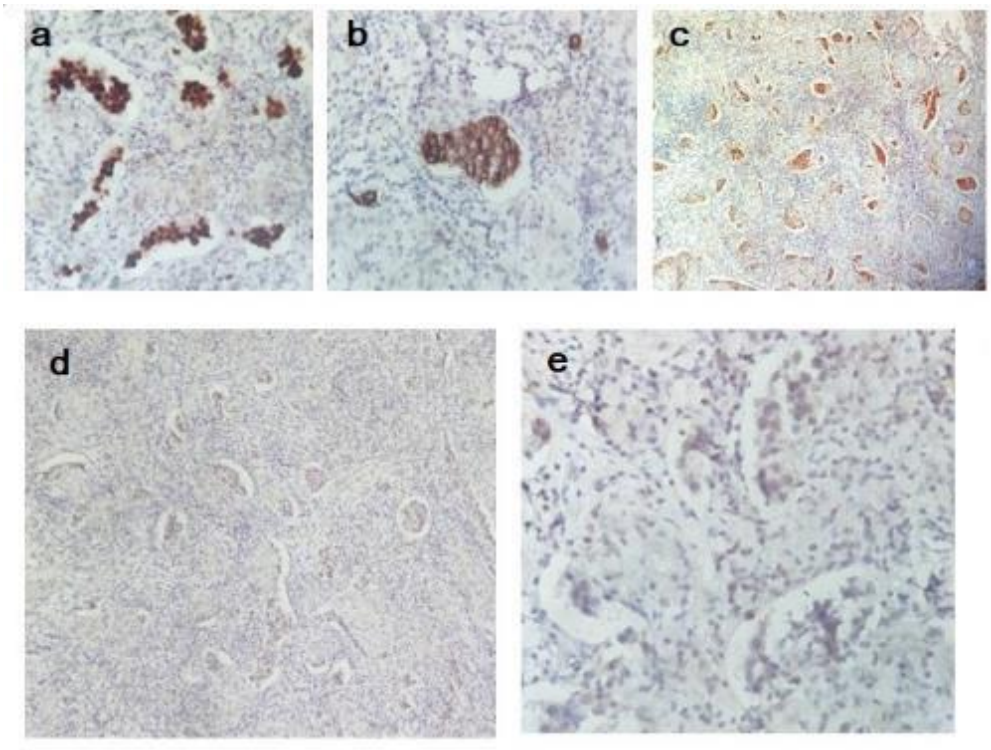

Figure 3. Immunohistochemical evaluation of the tumor cells, revealing nuclear positivity of SALL4 (×400) (a) and OCT3/4 (×100) (b) and membranous and cytoplasmic positivity of PLAP (×400) (c); negative CD30 (×100) (d) and AFP (×400) (e), respectively