

CASE REPORT

Malignant Mixed Germ Cell Tumor in a Patient with Swyer Syndrome: A Case Report

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Abstract

Mixed germ cell tumors are extremely rare tumors, usually malignant with a poor prognosis and made up of at least two different germ cell tumors. These tumors occur most often in the gonads but may also occur at other sites in body. In this case, a 24 year female presented to SMGSH, GMC Jammu with an abdominal lump associated with pain and primary amenorrhea. On examination, a firm mass reaching upto epigastrium was present. Upon investigation, all the tumor markers were raised. Her radiological evaluation showed a complex solid-cystic adnexal mass suggestive of neoplastic etiology. Simultaneously, patient was also evaluated for primary amenorrhea and upon karyotyping, she had an XY chromosome suggestive of Swyer syndrome. Patient underwent laparotomy with bilateral salpingo-gonadectomy and pelvic lymphadenectomy with preservation of the uterus. Histopathology confirmed mass to be a malignant mixed germ cell tumor with elements of teratoma, yolk sac tumor, and embryonal carcinoma.

Keywords

Swyer Syndrome, SRY gene, Malignant mixed germ cell tumor

Introduction

Swyer syndrome is a rare, distinctly different genetic disorder of sexual development characterized as a condition affecting sexual organ development (DSD, pure gonadal dysgenesis, 46 XY). The reported incidence is 1:80,000^[1]. In Swyer syndrome, people with one X and one Y chromosome, (present in males), are born with female external genitalia and underdeveloped gonads (ovaries or testes) known as streak gonads. Most people with Swyersyndrome due to their appearance are raised as females and are infertile. Despite the presence of a Y chromosome, the phenotype is female because dysgenetic (streak) gonads produce neither AMH nor androgens. These people have phenotypically female external genitalia with internal Mullerian duct structures but no

Wolffian duct structures. The uterus is small or rudimentary. Fallopian tubes are normal or reduced in size. Vagina may be normal or reduced in its length. The gonads are non-functioning dysgenetic streaks.

Usually, the cause is unknown. In at least 10-15% of the affected individuals, a mutation of the SRY gene that is located on the short arm of the Y chromosome (Yp11.3) is the cause. Due to pure gonadal dysgenesis, such patients are more likely to develop germ cell tumors due to the presence of the Y chromosome. Malignant germ cell tumors are rare tumors and have a poor prognosis. Usually, the patient with this syndrome presents late to the healthcare provider and even later to the expert for the evaluation of amenorrhea, infertility or even

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malignancy. It is a challenge to diagnose Swyer syndrome due to complex clinical presentation, laboratory, and imaging findings with only confirmative diagnosis upon karyotyping. Early diagnosis and proper management is the key to diminishing the risk of developing germ cell tumors.

Case Report

We present here the case report of 24 years old unmarried girl who was admitted to SMGS Hospital, Government Medical College on 28th Jan 2023 with chief complaints of amenorrhea, abdominal lump, pain abdomen, loss of appetite, and weight loss since 6 months. She had vague pain, insidious in onset, intermittent, associated with nausea and vomiting. There was no other significant personal, past or family history. On general examination, the patient was average build, well-oriented to time, place and person with secondary sexual characteristics corresponding to Tanner stage 2. Her vitals were within normal limits. There was no pallor, icterus, cyanosis, clubbing, or lymphadenopathy and there was no pedal edema. On Examination her BMI was 19.13 kg/m². Her abdomen was distended grossly. On palpation, a firm large mass corresponding to 36 weeks of gestation reaching up to epigastrium was present, it was immobile and non-tender, and there was no clinical ascites. Her Baseline investigations were within normal limits. CA 125 level was 136.10 U/L, CA 19-9 >500, BETA HCG 359.20 milliIU/ml, CEA 19.71ng/ml, LDH 459 U/L, AFP > 1000 ng/ml. On USG, a large ill-defined complex heterogenous adnexal mass with solid-cystic areas extending into the abdominal cavity upto epigastrium suggestive of neoplastic etiology was found. CECT revealed a large heterogeneously enhancing, pelvico-abdominal mass measuring (30x25x13 cm) possibly arising from the left adnexa with multiple internal necrotic areas, foci of calcification, and cystic spaces causing mass effect on major vessels(aorta/IVC), uterus, bladder, bowel loops and bilateral ureters with dilatation of bilateral pelvicalyceal system likely suggestive of Germ Cell Tumor – immature teratoma. CECT also demonstrated presacral, internal, and external iliac, inguinal, and mesenteric lymphadenopathy. The patient underwent exploratory laparotomy. On exploration, a 28x23x12 cm size mass was seen arising from left-sided gonadal tissue (streak gonad). The right gonad was also streak and was separate from the mass. Bilateral fallopian tubes appeared normal in appearance. The uterus was rudimentary and non-communicating with the vagina. There was minimal ascites and lymph nodes were not palpable. The whole

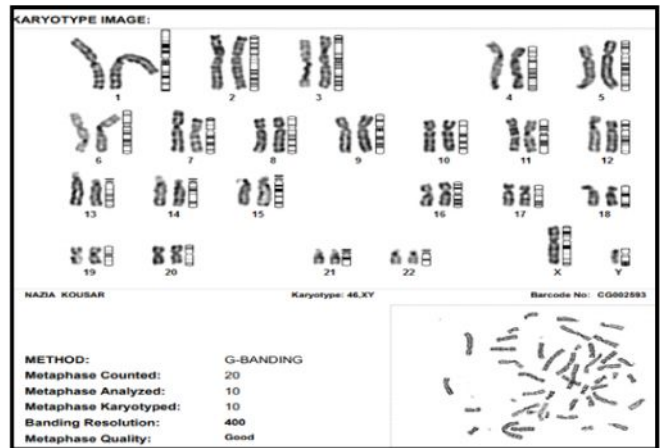


Fig1: Karyotyping of our case

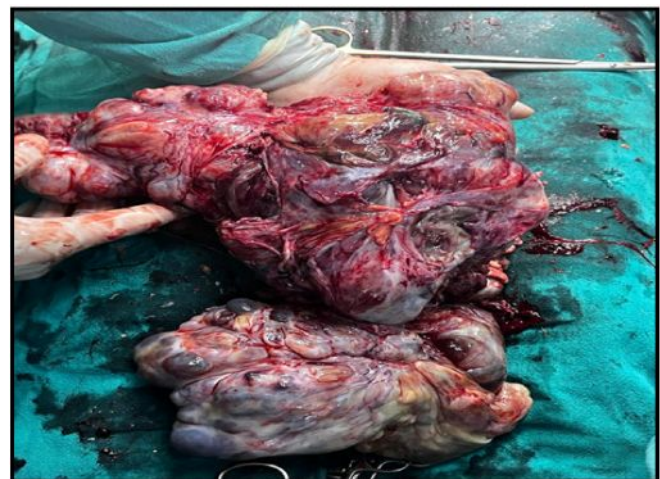


Fig 2: Malignant Germ Cell Tumor with Solid Cystic Gross Appearance

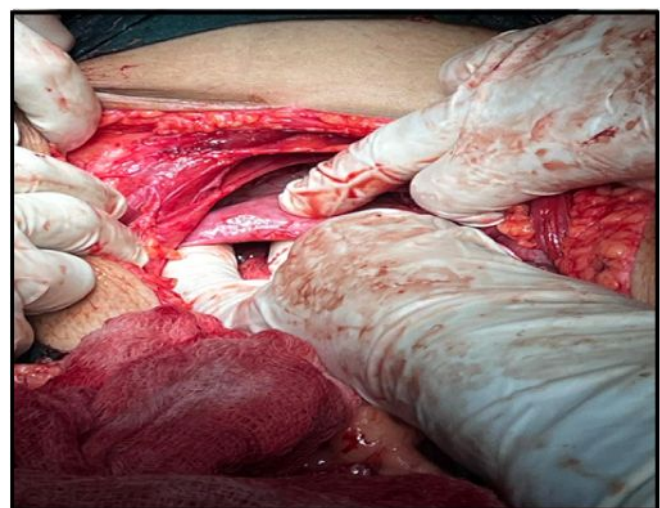


Fig 3: Image Depicting Rudimentary Uterus

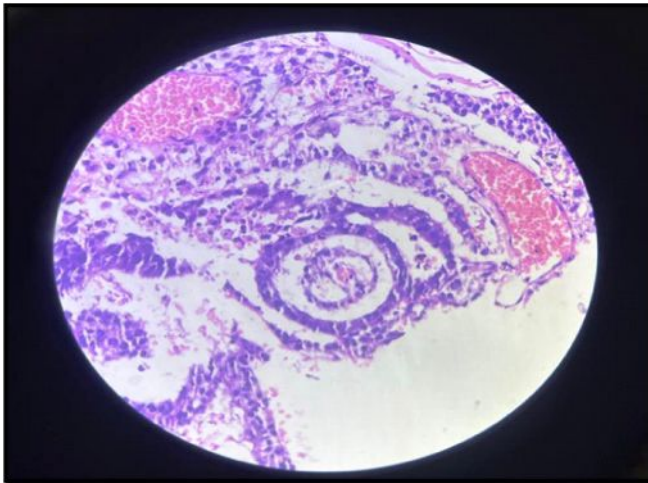
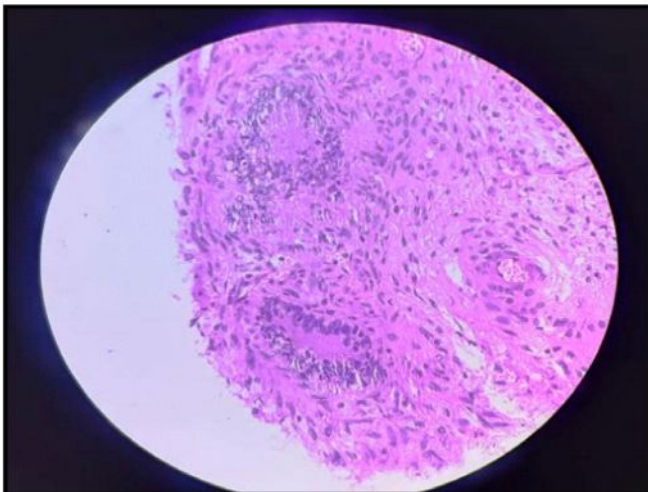


Fig 4: Histological Appearance of the Tumor
a. Figure showing immature epithelial component along with yolk sac component (H&E 40X)



b. Figure showing primitive neural tissue depicting rosette formation (H&E 40X)

mass was removed with difficulty as it was adherent to the large bowel superficially on its posterior surface. An intraop frozen section was performed to rule out a malignant tumor. Upon that, the tumor was found to be an immature teratoma. But since the gross appearance of the mass was giving the suspicion of malignancy and the patient was already a diagnosed case of Swyer syndrome, therefore we decided to perform bilateral salpingo-gonadectomy with preservation of the uterus. Omentectomy and pelvic lymphadenectomy were also performed. On gross examination, the tumor measured 28x23x12 cm and weighed 3.5 kg. The outer surface was irregular, and congested and showed solid-cystic

areas. The HPE report revealed tumor mass composed of different neoplastic germ cell elements – mainly teratoma with a poorly differentiated neuro-epithelial element at places forming rosettes; yolk sac tumor and embryonal carcinoma. Hence the diagnosis of a Malignant Mixed Germ Cell Tumor was made. Upon HPE, the bladder peritoneum and omentum showed no tumor deposits. Bilateral fallopian tubes, streak gonads, and pelvic peritoneum had carcinomatous deposits on HPE. Lymph nodes were negative for deposits.

Discussion

In this case, patient came with an abdominal lump with primary amenorrhea. Upon karyotyping, the patient was found to have Swyer syndrome. Swyer syndrome is a rare disorder of sexual development that was first described by Jim Swyer in 1955^[2].

DSDs arise from a number of genetic lesions, which manifest as a spectrum of gonadal (gonadal dysgenesis to ovotestis) and genital (mild hypospadias or clitoromegaly to ambiguous genitalia) phenotypes^[3]. In at least 10-15% of the affected individuals, it is caused by a mutation in the SRY gene due to deletion in the DNA-binding region of the SRY gene. In the remainder, no cause can be determined, although mutations in the SRY regulatory elements or other genes involved in the testis-determining pathway have been implicated (SF1, SOX9, WT, CMRT).

King & Conway also attributed 46,XY gonadal dysgenesis, due to mutations involving sex determining region Y, NR5A1, DHH or testis-determining gene loss-of-function mutations, DAX1 or WNT4 duplication or MAP3K1 gain-of-function mutations^[4].

Swyer syndrome usually presents itself with primary amenorrhea. This syndrome is characterized by a phenotypic female with female external genitalia, gonadal dysgenesis (bilateral streak gonads), and Mullerian structures. On karyotyping, 46XY is detected. All these findings were also present in our patient.

The differential diagnosis includes Mayer–Rokitansky–Küster–Hauser syndrome (XX), Congenital Androgenic Insensitivity Syndrome, 46 XX Gonadal Dysgenesis, and true hermaphrodites.

MRKH is a common cause of primary amenorrhea with the incidence being 1 in 5000. In MRKH there is variable degrees of Müllerian duct aplasia with aplasia of the vagina and a rudimentary or absent uterus. But contrary to Swyer syndrome, they have normal secondary sexual characteristics and a normal female karyotype (46, XX). Despite the male karyotype, the patients with Swyer

syndrome must be assured of their female gender identity and reassured regarding their ability to achieve and sustain a normal life. They can conceive using donor oocytes and artificial reproductive techniques^[5].

Another differential diagnosis is that of Congenital Androgenic Insensitivity Syndrome. In Congenital Androgenic Insensitivity Syndrome, the karyotype is XY with a high testosterone level. These patients are phenotypically females with presence of normal, yet undescended testis, absent Mullerian structures, and normal breast development. On the other hand, in Swyer syndrome, the breasts are usually underdeveloped with low testosterone levels as seen in our case.

At times, true hermaphrodites can also present with a female phenotype creating a diagnostic confusion with Swyer syndrome. But true hermaphrodite patients, have ovo-testis or a combination of an ovary and testes.

Because of the Swyer syndrome presence of the Y chromosome, patients with pure gonadal dysgenesis XY are at a higher risk of developing germ cell neoplasms incidence being 20-30%^[6]. Gonadectomy is advised due to the increased risk for malignant transformation in occult testicular elements.

Gonadoblastoma and dysgerminoma are the most common germ cell tumors in patients with Swyer syndrome. Gonadoblastoma is a premalignant germ cell tumor with undifferentiated cells unique to intersex states like Swyer syndrome and may contain or give rise to other highly malignant tumors including dysgerminoma, endodermal sinus tumor, embryonal carcinoma, and choriocarcinoma. Dysgerminoma (incidence 50-60%), is malignant and arises from the primordial germ cells identical to testicular seminoma. Smith *et al.* (2006) report incidence of dysgerminoma to be around 32.8%^[7].

Upon imaging, dysgerminoma appears as a multi-lobulated mass with fibro-vascular septa and speckled calcifications. Similar findings were found in our patient upon radiological examination.

Conclusion

Swyer syndrome is a rare disorder of sexual development that necessitates a meticulous clinical, laboratory, and

radiological evaluation. Clinically, the patient will present after the expected time of puberty with primary amenorrhea with or without a tumor with a female external phenotype. Upon karyotyping, the patient will have an XY chromosome. In cases with concomitant tumors, ultrasonography is the primary imaging modality which is usually aided by CT and MR imaging. MRI helps in the detection of the exact site of streak gonads and the characterization of lesions whereas CT is useful in detecting calcification and the nature of tumor. Though usually reported late, early diagnosis of Swyer syndrome is crucial as prophylactic gonadectomy in these cases reduces the risk of developing germ cell tumors.

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Conflicts of Interest

There are no conflicts of interest.

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