



Case report

Metastatic dysgerminoma in a young patient with 46 XY DSD: A rare case report

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ABSTRACT

The term DSD (Disorders of Sex development) is used to define those conditions in whom disharmony exists between chromosomal, hormonal and anatomical sex. Parental and patient mental health and quality of life are adversely affected by these conditions. Moreover, individuals with an underlying DSD, especially those with specific Y chromosomal material in their karyotype have an increased risk for developing a germ cell tumor. Here, we present a unique case of 46XY DSD with bilateral dysgerminomas presenting with abdominal mass at the age of 24 years, who was treated with one cycle of chemotherapy comprising of Carboplatin and Etoposide, following which he developed tumor lysis syndrome and later underwent exploratory laparotomy.

1. Introduction

Disorders of Sex development (DSD) are congenital conditions of incomplete or disordered gonadal development leading to discordance between genetic sex, gonadal sex, and phenotypic sex (Hughes et al., 2006). Estimated incidence of DSD is 1:5000 (Hughes et al., 2006). Individuals with an underlying DSD, especially those with specific Y chromosomal material in their karyotype have an increased risk for developing a germ cell tumor/cancer (GCC) (Cools et al., 2006). GCCs arise from primordial germ cells (PGC) and can be subdivided into seminomas/dysgerminomas and non-seminomas with carcinoma in situ (CIS) or gonadoblastoma (GB) as precursor lesions (Oosterhuis and Looijenga, 2005; Hersmus et al., 2008). GCC risk varies, but is estimated to be over 30% in patients with complete gonadal dysgenesis and is often bilateral (Cools et al., 2006). DSDs significantly impact individuals and their families due to their sensitive nature and stigma surrounding gender identity and gender roles. Due to several sociocultural factors, individuals who reside in developing countries with limited access to healthcare are affected more adversely.

1.1. Case study

This patient had ambiguous genitalia at birth. He was reared as a male without any further evaluation. However at the age of 10 years, he noticed bilateral breast development with increase in size of phallus. Two years later, he developed cyclical hematuria. He used to bleed for 2,3 days while passing urine every month. Health care consultation was not taken due to social stigma and fear. Now at the age of 24 years, patient presented with history of abdominal pain and abdominal mass for two years. There was history of loss of weight and appetite. His height was 165 cm and weight was 48 kg. On examination, per abdomen, a large, movable, abdominopelvic mass measuring 15 × 18 cm extending upto epigastric region was palpable. On local examination microphallus of size 4 cm without urethral opening was seen. Urethra was located 4 cm below the microphallus. Labia majora and labia minora were completely fused as shown in Fig. 1. Bilateral gonads were not palpable.

On laboratory assessment, complete blood count, urinalysis, renal and liver function tests, serum and urine electrolytes, and thyroid function tests were in normal range. Hormonal profile showed low testosterone, dehydroepiandrosterone sulphate (DHEAS) and anti-mullerian hormone (AMH) levels. Leutenizing hormone (LH), follicle

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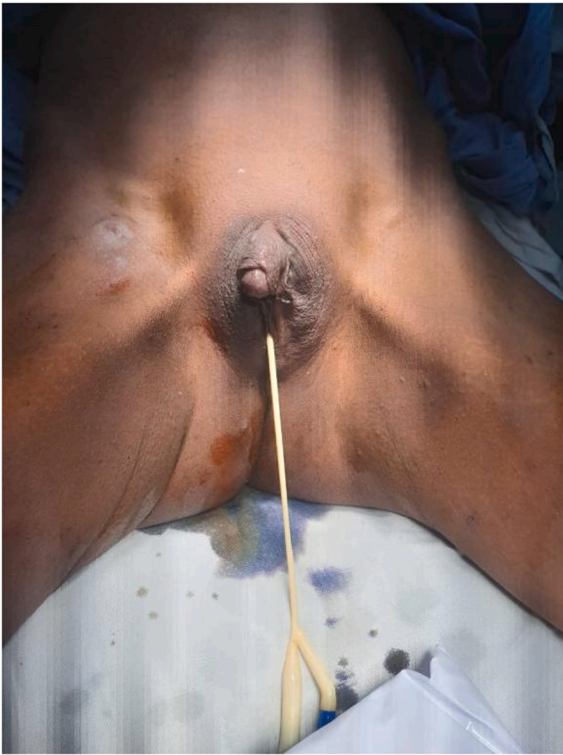


Fig. 1. External genitalia with urinary catheter insitu.

stimulating hormone (FSH) and estradiol (E2-17B was 75.9) were within normal limits. On further evaluation, MRI (Magnetic resonance imaging) showed uterus and two well defined abdominopelvic masses (14.4cmx8.5 cm and 15cmx9cm) with possible gonadal origin based on blood supply. During hospital stay LH surge was seen which was followed by hematuria. This suggests he had functional ovaries with low ovarian reserve as suggested by low AMH. Beta HCG, CA19-9, AFP, CEA were normal but CA125 (128.6) and LDH (600) were elevated. His genitogram was inconclusive. PET-CT showed multiple FDG avid lymph nodes in the abdomen (periportal and mesenteric lymph nodes), mediastinum, neck, left axilla, and diaphragm. FDG avid bilateral lung lesions were noted. On karyotyping (GTG-Banding with Trypsin and Giemsa stain), 20 metaphases were analyzed, all cells showed 46 XY.

An ultrasound guided FNAC from abdominopelvic mass showed aggregates of tumor cells having vesicular chromatin, prominent nucleoli, in a tigroid background. In addition, many scattered sarcoid like granulomas admixed with lymphocytes and occasional multinucleated giant cells were also noted. Immunocytochemistry done on the cell block showed that these tumor cells were positive for SALL4 and OCT4 while negative for CD30 and AFP, suggestive of dysgerminoma as shown in Fig. 2.

Diagnosis of DSD with possibility of ovotesticular or mixed gonadal dysgenesis with metastatic gonadal dysgerminoma was made. A comprehensive psychology analysis regarding gender identity was done and patient wished to remain as a male. In view of COVID induced disruption of normal oncology practice, neoadjuvant chemotherapy (NACT) comprising of Carboplatin and Etoposide (Carboplatin-450 mg and Etoposide-200 mg) was started. However, following the first cycle of chemotherapy only, he developed febrile neutropenia along with renal failure. Blood and urine culture showed growth of *Escherichia coli*. In

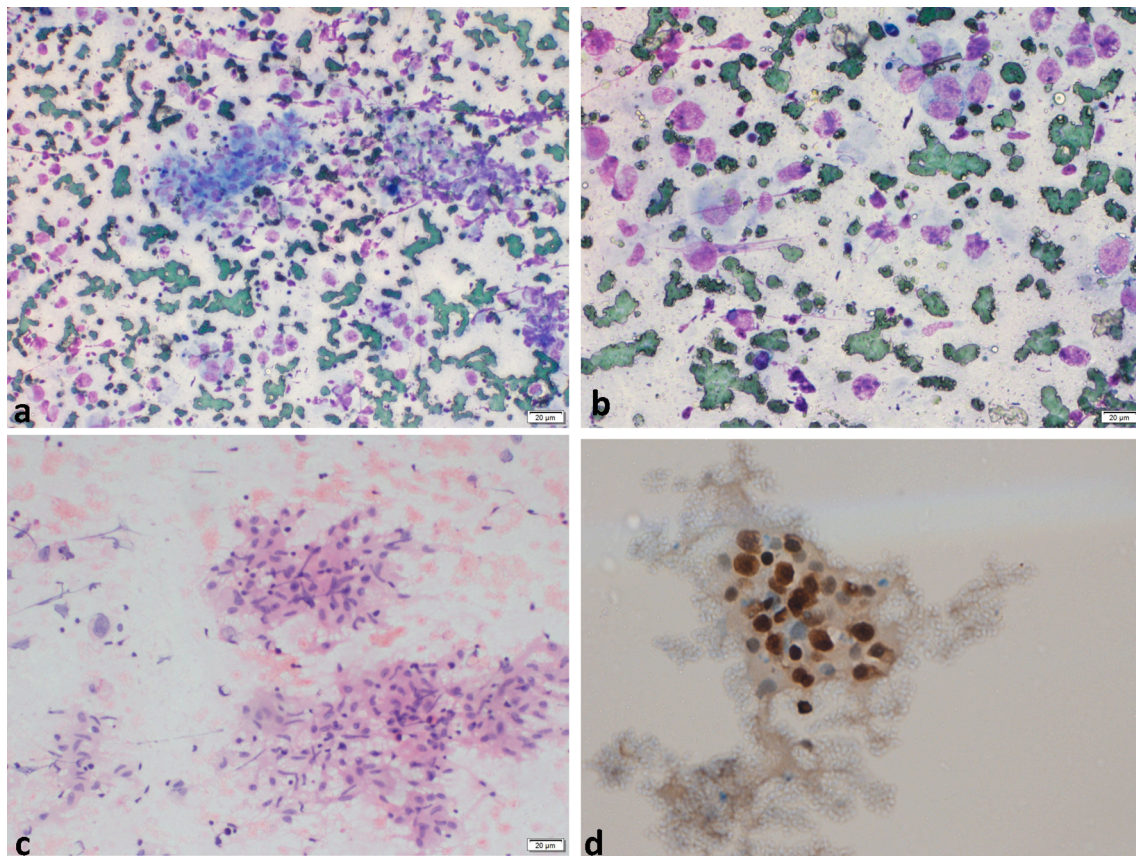


Fig. 2. (a) Cytology smears showing singly scattered as well as small cohesive clusters of tumour cells. (b) Tumor cells showing vesicular chromatin, prominent nucleoli and moderate amount of cytoplasm. (c) Smears showing many scattered sarcoid like granuloma admixed with lymphocytes and occasional multinucleated giant cells. (d) Cell block section showing nuclear positivity for OCT-4 in tumor cells. (a-b MGG;c-H&E;d-IPOX).

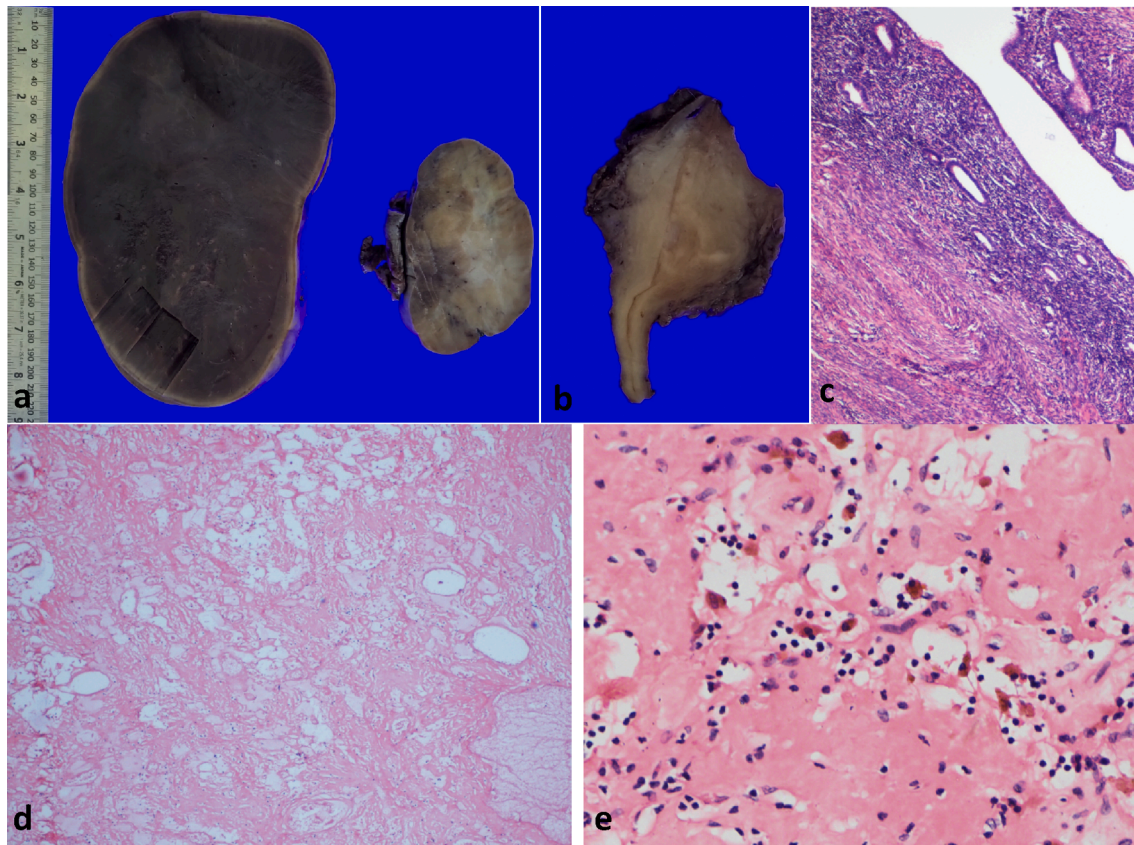


Fig. 3. (a) Gross image of bilateral adnexae showing homogenous soft reddish brown mass in the larger mass and grey white firm areas in the smaller mass. (b) Small sized uterus measuring $4 \times 3 \times 1$ cm. (c) sections from uterus showing Endometrium in proliferative phase (d-e) sections from bilateral adnexa showing large areas of infarction necrosis, hyalinisation admixed with mixed inflammatory cells and pigment laden macrophages.

view of neutropenia, he was given G-CSF (Granulocyte-colony stimulating factor) 5 mcg/kg for four days following which he had an increase in total leucocyte count. In view of renal insufficiency (urea/creatinine 195/7.5) along with hyperkalemia, three sessions of hemodialysis were given. Possibility of tumor lysis syndrome and sepsis related AKI (Acute kidney injury) was considered. So further chemotherapy was deferred. He was again admitted after one month with complaint of severe abdominal pain and fever. On examination, there was a tender mass with guarding and rigidity. CECT (Contrast enhanced computed tomography) abdomen revealed large abdominopelvic mass with calcification and areas of high attenuation suggestive of haemorrhage. Suspicion of hemorrhage, infection and torsion in the mass was very high. Parenteral antibiotics, analgesics were given and after stabilization exploratory laparotomy was done.

Intraoperatively, omentum was adherent to the mass and covering it completely. Omental adhesions were separated. A twisted mass of $15 \times 11 \times 8$ cm size arising from left gonad was seen, which was necrosed. Another mass of size $10 \times 6 \times 4$ cm seen on right side arising from right adnexa. Uterus was small in size measuring $4 \times 3 \times 1$ cm and cervix was long and tubular measuring 5×1 cm extending upto pelvic floor. Bilateral tubes were normal. Gut loops were distended and adherent to the mass. There was constriction of gut at the point of adhesion at approximately 10 cm distal to duodenojejunal junction. Adhesiolysis was done and contents aspirated from gut through Ryles tube by retrograde milking of gut. Bilateral adnexal masses were excised after de-torsion of left adnexal mass. Subtotal hysterectomy was done and 2–3 cm of cervix was left behind. Infra-colic omentectomy was done. Pelvic and retroperitoneal lymph nodes were not enlarged and suspicious. Post operative period was uneventful and patient discharged under stable condition.

On histopathology examination, the cut sections of the larger mass

revealed homogenous reddish brown soft areas with no viable or normal ovarian parenchyma. The smaller mass revealed grey white firm areas. Multiple sections examined from bilateral adnexal masses showed extensive areas of infarction, necrosis, haemorrhage, foci of calcification and collection of hemosiderin laden macrophages. No viable tumor or normal ovarian parenchyma identified. Sections from the uterus and fallopian tube were unremarkable. Sections from the omentum showed extensive mesothelial cell proliferation, areas of haemorrhage, fibrosis, mixed inflammatory cells along with many hemosiderin laden macrophages. No viable tumor cells were seen as shown in Fig. 3.

Our further plan is to administer atleast two more cycles of chemotherapy and later perform a genital reconstructive surgery in this patient.

2. Discussion

Genital ambiguity is seen in 1 in 5000 births (Hughes et al., 2006). The term DSD issued to define those congenital conditions in which disharmony exists in between chromosomal, hormonal and anatomical sex (Hughes et al., 2006). DSDs have been classified on the basis of sex chromosome. Our patient has 46, XY DSD. It could be either ovotesticular or mixed gonadal dysgenesis type.

In ovotesticular DSD, both Mullerian and Wolffian duct derivatives are present in the same individual and the genitalia are of ambiguous nature (Swain et al., 2014). A variety of phenotypes is seen of both external and internal genitalia. Most of these patients have a well-formed uterus present (Swain et al., 2014). The gonads may be ovotestis or a combination of ovary on one side and testis on the other. These patients are usually reared as male because of the size of the phallus and labioscrotal fusion which is of varying degrees. At puberty, feminization and menstruation occurs. Various chromosomal

abnormalities have been described in these individuals and include 46, XX, 46,XY, 46,XX/46,XY, 47,XXY, 47,XYY, 45X, and 46,XX/47,XXY mosaicism. 90% of the patients have 46 XX karyotype and 10% of patients have 46XY karyotype as seen in our case (Donahoe and Schnitzer, 1996).

Mixed gonadal dysgenesis is characterized by a unilateral testis (often intra-abdominal), a contra-lateral streak gonad, persistent Mullerian duct structures and various degrees of inadequate masculinization. The most common karyotype is 45,XO/46,XY, other mosaics have also been reported with structurally normal or abnormal Y chromosome.

Our patient had characteristics of ovotesticular DSD but we do not have histological evidence of ovotestes, which may be because of chemotherapy induced necrosis of gonads, as dysgerminoma is highly chemosensitive tumor.

Patients with Y chromosome or Y-derived sequences are at increased risk (10–30%) of developing gonadal tumors (Verp and Simpson, 1987). The most common neoplasm is a Germ cell tumour, with dysgerminoma being the most common histological type. Our patient had FNAC based diagnosis of germ cell tumor with ICC suggesting dysgerminoma. He received one cycle of NACT with EP (etoposide and carboplatin) due to covid pandemic. There was a remarkable response to NACT suggested by histopathology findings post-operatively. This highlights highly chemosensitive nature of dysgerminoma. In a series of NACT for OGCT (Ovarian germ cell tumor), Talukdar et al. presented 23 cases from 1988 to 2009 in which patients with stage III and IV malignant OGCT received four cycles of BEP NACT (Talukdar et al., 2014). Dysgerminomas accounted for 14 cases. Twenty-one patients with OGCT experienced either a complete response (CR) or partial response (PR), of whom 12 had dysgerminoma. All 21 patients were alive and disease-free. Authors compared this to 43 cases over the same time period that were treated with surgery followed by chemotherapy. Thirty-four patients had greater than 2 cm of residual tumor. Of these 43 patients, 30 were alive and disease-free at analysis (Talukdar et al., 2014). Their findings suggest that NACT resulted in better survival. Our case supports the use of NACT in patients with metastatic dysgerminoma, provided there is careful monitoring for risk of tumor lysis syndrome.

Careful evaluation and early diagnosis of DSDs are very important. However, the optimal protocol of management for DSD patients remains controversial (Crone et al., 2002). Some tertiary health care centers have a multidisciplinary DSD team that addresses the psychological, medical, and surgical needs of children and adolescents with DSD and their families. The team often includes pediatric providers in psychology or psychiatry, genetics, gynecology, endocrinology, surgery, and urology as well as social work and nursing support. Treatment in cases of DSD may involve medical treatment, surgical correction of ambiguous

genitalia and removal of dysgenic gonads or mullerian components, and psychological counselling, especially in patients who have presented during their adolescence or adulthood (Hughes et al., 1958¹). Educating medical and paramedical staff is crucial to ensure adequate early assessment, diagnosis, counselling and appropriate management.

3. Conclusion

Early detection and referral of a patient with ambiguous genitalia can provide improved quality of life, and prevent gender dysphoria and psychosocial dilemmas. Prophylactic removal of the dysgenetic gonad may prevent risk for malignant transformation.

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The manuscript has not been published previously and is not under consideration elsewhere.

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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