Germ Cell tumors in Disorders of Sex Development (DSD)- a Case Report.

RAJA G GOPAL
Department of Medical Oncology,
MADRAS MEDICAL COLLEGE AND GOVERNMENT GENERAL HOSPITAL

Abstract:
Disorders of Sex Development (DSD), previously known as intersex, refer to congenital conditions in which development of chromosomal, gonadal or anatomical sex is atypical. Patients with specific variants of this disorder have an elevated risk for the development of so-called Type II Germ Cell Tumors i.e Seminomatous and Non-Seminomatous tumors, referred to as germ cell tumors, especially in patients with DSD and Gonadal Dysgenesis or Hypovirilization are at risk. In this article we present one such rare case of germ cell tumor in a patient presented with DSD to our department. This article also discusses the literature review on DSD and the risk of gonadal malignancy.

Keyword: Disorders of Sex Development (DSD), Type II Germ Cell Tumor, Gonadal dysgenesis, Hypovirilization.

INTRODUCTION:
Disorders of Sex Development (DSD) or intersex disorders refer to conditions of incomplete or disordered genital or gonadal development leading to discordance between genetic sex, gonadal sex, and phenotypic sex (1). The so-called “type II germ cell tumors of the testis and the dysgenetic gonad” are by far the most frequently occurring and feared tumors in patients with DSD. However, sporadically, other gonadal (benign and malignant) neoplasms are reported in patients with DSD, often in combination with the above mentioned type II germ cell tumors. These include sex cord (SC)-stromal tumors [juvenile granulosa cell tumor (2), Sertoli-Leydig cell tumor (3), and Sertoli cell nodules (4-6)] and epithelial tumors [Brenner tumor (7), mucinous cystadenoma (2, 7), and Mullerian cyst (4)]. The invasive type II germ cell tumors that are encountered in the intersex gonad are the seminoma (if the gonad is considered a testis)/dysgerminoma (DG) (if the gonad is considered an ovary) and the nonseminoma. The development of these invasive tumors is always preceded by the presence of an in situ neoplastic lesion—intratubular germ cell neoplasia unclassified (ITGNU) or gonadoblastoma (GB). In this article we present one such case of DSD who developed germ cell tumor and literature review on DSD and the risk of gonadal malignancy.
CASE REPORT:
A 38 year old phenotypically female had a history of swelling in the left side Inguino- labial region since 2 yrs. She has not attained menarche so far and unmarried. On examination she had normal breast development and pubic hair growth. The primary physician found a 15*15 mass seen in the left Inguino-labial region with variable consistency, also found a gonad in the right inguino-labial region. The external genitalia had hypertrophied clitoris, ill developed labia minora bilaterally and a blunt vagina. The CT scan abdomen and pelvis report revealed absent uterus and ovaries with a huge heterodense mass in the left inguno-labial region with evidence of fluid within the doubtful scrotal sac. No Para-aortic nodal enlargement. Karyotyping was done to know her chromosomal sex and it turned out to be 46XY, and Barr body was absent. Fine Needle Aspiration Cytology (FNAC) from the left inguino-labial region reported as malignancy probably Seminoma. Tumour markers were elevated (LDH-2860 IU, sr. -HCG – 29.9 mLU/Land -FP – 3.8 ng/ml). Finally she was diagnosed as Male Pseudo-Hermaphroditism with germ cell tumour of left testis. She underwent bilateral high inguinal orchidectomy. Post op HPE showed Mixed Germ Cell Tumor with prominent Seminomatous component and a minor yolk sac component.

With this history and diagnosis, patient was referred to our department and she has been staged as TX,NX,M0, Good risk. She was treated with 4 cycles of EP on MARCH 2011. Post chemotherapy disease evaluation showed normal abdominal and chest CT imaging and normal tumor markers. She is on follow up since then. The last follow up was on February 2014 and she is doing well.

LITERATURE REVIEW
Patients with specific forms of disorders of sex development (DSD), as defined recently in the Consensus Statement on Management of Intersex Disorders(8), have an increased risk for development of cancers originating from the germ-cell lineage, also known as germ-cell tumors (GCTs)(Table 1). The incidence of germ cell tumors is increased in patients with DSD containing Y chromosome material in their karyotype and is probably related to the presence of the TSPY gene. The ectopic position of the (dysgenetic) testis adds to this risk because the prevalence of germ cell tumors in simple cryptorchidism is estimated at four to 10 times the normal incidence of 6–11 per 100,000 (9, 10, 11). The actual classification system of DSD is based on phenotypic, genetic, and pathological criteria at the same time and shows several overlaps (Table 2). For this purpose, intersex patients were divided into three major groups, based on a common underlying pathophysiological mechanism per group. They are hypervirilization syndromes, undervirilization syndromes and gonadal dysgenesis syndromes. Patients with hypervirilization syndromes are not at risk for the development of germ cell tumors. The gonadal tissue always consists of well-differentiated ovaries, and the chromosomal constitution is 46,XX. Among the undervirilization group, patients with Male pseudo-hermaphroditism, combined series reveal a tumor prevalence of 2.3% (in a series) (13, 14–16). Although data are limited, the risk seems to be markedly higher in the partial Androgen Insensitivity syndrome (PAIS) [in a series -15%] (6) than in the complete Androgen Insensitivity Syndrome (CAIS) [in a series-0.8%] (2, 6, 13).
Tumor prevalence in AIS markedly increases after puberty and reaches 33% at the age of 50 yr (13). Gonadal dysgenesis (GD) is defined as an incomplete or defective formation of the gonads, as a result of a disturbed process of migration of the germ cells and/or their correct organization in the fetal gonadal ridge. Structural or numerical anomalies of the sex chromosomes or mutations in genes involved in the formation of the urogenital ridge and in sex determination of the bipotential gonad mostly underlie these disorders (2, 58–61).

Four series report on the prevalence of germ cell tumors in GD (not further specified): A germ cell neoplasia is found in 21% (13, 14, 17, 18). In selected series of patients with true hermaphroditism, the prevalence of tumors is considerably lower. In three studies, it was 2.6% (14, 16, 19). Summary of the estimated germ cell tumor prevalence in patients with DSD and type of precursor lesion is given in Table 3. A set of relevant immune-histochemical markers (OCT3/4, PLAP, c-KIT, TSPY, VASA) was specifically examined in large series of gonads from intersex patients. The markers OCT3/4, c-KIT, and PLAP show overlapping expression patterns, but the use of the newer (both monoclonal and polyclonal forms of) OCT3/4 results in a well-circumscribed and intense nuclear staining, is easiest for interpretation. From Table3, it becomes apparent that Carcinoma In-situ (ITGCNU) is the almost exclusive precursor lesion in undervirilized patients, whereas Gonadoblastoma is predominant precursor lesion in patients with Gonadal Dysgenesis. Pathogenesis of progression into malignancy in the testes of patients with undervirilization syndromes and GD,is that OCT3/4-positive PGCs/gonocytes manage to make contact with the basal lamina and seem to definitively escape down-regulation of OCT3/4 and further differentiation along the spermatogenic pathway. These OCT3/4-positive and TSPY-positive germ cells in contact with the basal lamina can now undergo mitotic proliferation and are prone to clonal expansion (figure 1). Based on the pattern and degree of differentiation of gonads, Cools et al proposed a new classification of patients with DSD and the risk of tumor development, given in the Fig2. The overall summary of the DSD conditions and their risk of developing malignancy and the recommended action needed for the conditions given in the Table 4.

In summary, Germ cell Neoplasms are common in patients with Disorders of Sex Development (DSD) especially Type II Germ cell tumours i.e Seminoma and Nonseminomas. Higher incidences are seen in the patients with Dysgenetic gonads than in patients with undervirilization (male pseudohermaphrodites). Patients with hypervirilization (female pseudohermaphrodites) are not at increased risk of developing malignancy. We have reported one patient with undervirilization who developed Mixed germ cell tumors

Figure 1. Demonstrates the pathogenesis of precursor lesion formation in hypovirilization and GD.(ref 20)
**PATOGENESIS OF PRECURSOR LESION**  
Figure 2, classification of patients with DSD and their tumor risk.

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**CLASSIFICATION OF PATIENTS WITH DSD AND TUMOR RISK**

CAH, Congenital adrenal hyperplasia; PHP, pseudohermaphroditism; AMH, anti-Müllerian hormone; StAR, steroidogenic acute regulatory protein; WT-1, Wilms’ tumor 1 gene; WAGR, Wilms’ tumor aniridia genitourinary anomalies and mental retardation; SOX9, SRY-box-related gene 9; SF-1, steroidogenic factor 1; hCG, human chorionic gonadotropin. Asterisks represent categories showing partial overlap.  

- **a** (Mostly ambiguous) phenotype resulting from the presence of bilateral dysgenetic testes.  
- **b** (Mostly ambiguous) phenotype resulting from the presence of bilateral dysgenetic testes or one dysgenetic testis on one side and a streak on the other side.  
- **c** (Mostly ambiguous) phenotype resulting from the presence of one dysgenetic testis on one side and a streak on the other side.  
- **d** Normal female phenotype (without Turner stigmata) in the presence of bilateral streak gonads (devoid of germ cells) in a 46,XX or 46,XY individual.  
- **e** (Mostly ambiguous) phenotype resulting from the presence of both testicular tissue consisting of seminiferous tubules and ovarian tissue, containing germ cells that are all enclosed in primordial and eventually growing follicles in the same individual, either in a single gonad or in opposite gonads.

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