

Malignancy in disorders of sex development

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Abstract: Disorders of sex development (DSD) represent a spectrum of conditions in which chromosomal, gonadal, or anatomic sex are atypical and affect 1 in 4,500–5,000 live births. The diagnosis of DSD raises concerns of tumor risk and treatment as well as future fertility preservation. We review the current understanding of the types of gonadal tumors that arise in DSD patients as well as possible markers and treatment. The goal is to inform the members of the DSD team (urologist, endocrinologist, geneticist, psychologist) of the latest findings regarding malignancy in DSD. PubMed[®] and Google Scholar[™] literature searches were performed of current and past peer-reviewed literature on DSD (intersex) regarding gonadal development and tumor formation/treatment. Relevant reviews and original research articles were examined, including cited references, and a synopsis of the data was generated. DSD patients are at increased risk for the development of testicular carcinoma in-situ (CIS) and germ cell tumors (GCT), including seminoma, non-seminoma, juvenile granulosa cell, gonadoblastoma, and dysgerminoma. Cancer risk factors include Y-chromosomal material and gonadal position, especially for streak gonads. The 46 XX DSD patients [congenital adrenal hyperplasia (CAH)] with no genetic Y-chromosomal material are not at higher risk of cancer. Post-pubertal complete androgen insensitivity syndrome (AIS) patients remain prone to tumor development if the testes remain in the abdomen. Estimates of the risk of GCT in partial AIS for untreated undescended testes may be as high as 50%. The cancer risk of scrotal testes in partial AIS is unknown. CIS occurs almost exclusively in patients with hypovirilization, most notably in AIS. Persistent Mullerian Duct Syndrome (PMDS) confers the usual cancer risk associated with cryptorchidism, but also a possible tumor risk of the Mullerian remnant. Several markers are under investigation for tumor evaluation in the DSD population beyond hCG and AFP (Oct3/4, TSPY, WT-1). The management of patients with DSD is complex and evaluation of tumor risk is aided by advances in genotyping for Y-chromosomal material not evident in traditional karyotyping. More complete genetic screening for DSD patients should increasingly become the standard of care. Developments in pathologic diagnosis will further challenge our traditional understanding of the oncologic management and surveillance of these patients. Future studies utilizing more advanced histologic examination of gonads will improve our understanding of the true incidences of malignancy in this diverse population.

Keywords: Disorder of sex development (DSD); malignancy; intersex; gonad; cryptorchidism

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Introduction

Disorders of sex development (DSD), formerly termed intersex disorders, represent a spectrum of conditions in which chromosomal, gonadal, or anatomic sex are atypical (1). They are estimated to affect 1 in 4,500–5,000 live births (2). Patients with DSD are often managed by an interdisciplinary team of clinicians including urologists, endocrinologists, geneticists, oncologists, and psychologists. From a urologic perspective, the diagnosis of DSD raises concerns of tumor risk and treatment as well as future fertility preservation. DSD patients are at increased risk for the development of testicular carcinoma in-situ (CIS) and germ cell tumors (GCT), including seminoma, non-seminoma and gonadoblastoma and dysgerminoma. Other tumors are also of concern, including juvenile granulosa cell tumors (JGCTs) and tumors of congenital adrenal hyperplasia (CAH) (3,4). Developments in pathologic diagnosis will further challenge our traditional understanding of the oncologic management and surveillance of this patient population.

DSD diagnoses

The categories of DSD according to the 2006 Consensus Group include 46 XX DSD, 46 XY DSD, ovotesticular DSD, and sex chromosome disorders. However, only 50% of patients with ambiguous genitalia will have a definitive diagnosis made (5). The 46 XX DSD (formerly female pseudohermaphroditism, or hypervirilization syndromes) refers to patients with two normal ovaries and masculinized external genitalia. Patients with congenital adrenal hyperplasia (CAH) comprise the majority of this category and are not at a higher risk of gonadal malignancy (4). The 46 XY DSD (formerly male pseudohermaphroditism, or undervirilization syndromes) involves two “normal” (often dysgenetic) testes and partial or complete feminization. The specific diagnoses within this category include: 5-alpha reductase deficiency, partial or complete androgen insensitivity, dysgenetic testes, primary testicular failure, Leydig cell failure and androgen biosynthesis defects. Ovotesticular DSD (formerly true hermaphroditism) involves gonads with both ovarian and testicular tissue, variable karyotype and variable external genitalia. Dysgenetic DSD involves poorly differentiated gonads, also with variable external genitalia and karyotype.

Chromosomal abnormalities

Cancer risk factors include Y-chromosomal material

and gonadal position. The relative risk of malignancy in undescended testes, regardless of DSD diagnosis, is estimated between 2.75 and 8 (6). With this in mind, 46 XX DSD patients (most commonly CAH) with no genetic Y-chromosomal material are not at higher risk of cancer. However, so-called “tumors of CAH” may present as testicular or paratesticular masses (adrenal rests) which are benign and often multi-focal, but may mistakenly be diagnosed as Leydig cell tumors (3). They are often associated with an increase in 17-hydroxyprogesterone level. MR or ultrasound may be helpful to confirm tumor extent. If confident of the CAH hyperplastic adrenal rest diagnosis, orchiectomy is not indicated. The nodules usually resolve with further steroid replacement.

Patients with Turner Syndrome, who are born with normal gonads but regress through apoptosis to bilateral streak gonads, may harbor Y chromosomal material in 3–39% of patients with a 45, X0 karyotype (3). The diagnosis of occult Y-chromosomal material may require further molecular analysis. Streak gonads are dysgenetic gonads that lack normal embryologic development and contain fibrous tissue and primitive ovarian structures. The results of a full genotype evaluation will determine the risk of malignancy and the need for prophylactic gonadectomy.

Patients with Klinefelter Syndrome (47XXY) typically have testicular atrophy, decreased androgen levels, and elevated gonadotropin levels. Despite this, several studies have shown that they are not at a higher risk for testicular GCT. This finding argues against the theory that testicular atrophy or raised gonadotropin levels are associated with a risk of testicular malignancy. However, men with Klinefelter Syndrome may be at substantially elevated risks for non-Hodgkin lymphoma, breast cancer, and possibly lung cancer—though the exact mechanisms remain unclear (7,8).

Juvenile granulosa cell tumor (JGCT), a tumor of sex cord-stromal cells, has been noted to occur in rare cases of sex-chromosomal mosaicism and ambiguous genitalia in the neonatal period. These tumors are benign and hormonally inactive so testis-sparing surgery should be curative (9).

Androgen insensitivity syndrome (AIS)

AIS, caused by an end-organ defect in the androgen receptor, results in undermasculinization, and are often with undescended testes. The variable development of Wolffian structures (vas deferens or epididymis) does not affect the risk of malignancy, which is low in adolescents. Pathologic

findings of gonads include testicular degeneration and dysplasia in one series of adolescent complete AIS patients. In that cohort, 2 of 44 patients (5%) developed GCT and both were post-pubertal (10). Another cohort of complete AIS patients found one pubertal patient (14 years old) of twenty-nine patients developed CIS, and to date without GCT formation (11). The only case of documented GCT in a pre-pubertal complete AIS patient is that of a 17-month-old girl with a metastatic yolk sac tumor in an abdominal testis which required adjuvant chemotherapy (12).

Post-pubertal complete AIS patients remain prone to tumor development if the testes remain in the abdomen—historical estimates place the risk of malignancy at 3.6% at 25 years and 33% at 50 years (13). In cohorts based on prophylactic gonadectomy, the incidence of GCT in partial AIS (usually AIS patients raised female) is significantly higher—15%, according to Cools *et al.* (4). Higher estimates of the risk of GCT in partial AIS for untreated undescended testes may be as high as 50%. The cancer risk of scrotal testes in partial AIS is unknown (1). Similarly, completely feminized patients with androgen biosynthesis defect—46 XY DSD—should undergo gonadectomy in childhood due to risk of testicular malignancy.

The standard of care remains orchiectomy, the timing of which (pre- or post-pubertal) remains controversial. The finding of the majority of tumors in the post-pubertal age group argues for later surgery while the treatment of associated inguinal hernia and psychological issues related to the gonad may warrant pre-pubertal surgery (1). The advantage of natural hormone production by the testes aiding in development of secondary sex characteristics is theorized though not substantiated by research trials. Estrogen replacement therapy is appropriate in nearly all of these patients.

Persistent Mullerian duct syndrome (PMDS)

PMDS was traditionally thought to confer only the risk associated with undescended testes. However, recent case reports show that the Mullerian remnant structures themselves are also a risk factor for malignancy, including adenocarcinoma. One literature review identified eleven cases of malignancy among 200 total PMDS cases. The authors propose that bilateral orchiopexies and laparoscopic excision of Mullerian remnant structures should be pursued. It has been recommended that patients with PMDS should undergo surveillance, though protocols for that are still under investigation (14).

Pre-malignant lesions

Gonadoblastoma (GB) is a lesion largely unique to patients with DSD. Pathologically, it presents with a mixture of germ cells and stromal elements as well as immature Sertoli cells and may contain calcifications. Approximately 80% of patients with GB are phenotypic females and 20% are phenotypic males (3), often presenting with hypospadias and undescended testes that are frequently bilateral (8). It is seen more commonly in post-pubertal patients and occurs almost exclusively in patients with dysgenetic gonads, requiring the presence Y-chromosomal genetic material (15). Invasion of stroma leads to a diagnosis of dysgerminoma (in females) or seminoma (in males), occurring in 50% of cases (3). However, pure gonadoblastomas are not metastatic. Dysgerminoma may metastasize but is responsive to radiation therapy (8). The incidence of GB in dysgenetic DSD varies from 4.7% to as high as 25% (16), likely owing to the persistent heterogeneity in diagnosis of the underlying DSD. Regardless, the overall tumor risk of dysgenetic DSD is between 15% and 33% (4). Discovery of GB is often made in the evaluation of primary amenorrhea leading to a diagnosis of Swyer Syndrome (46 XY complete gonadal dysgenesis). The treatment is radical gonadectomy. However, the pathophysiology, natural history and predictive factors behind malignant transformation remain to be elucidated (17).

CIS (or intratubular germ cell neoplasia, ITGCN) is a congenital lesion which may progress to GCT. Under the testicular dysgenesis syndrome hypothesis, germ cells undernourished by Sertoli cells are developmentally delayed and at high risk for infertility and tumor formation (4). CIS progresses to invasive disease in 50% of patients within 5 years (18), however the natural history in adolescents is less clear. Pathologically, CIS appears as fetal gonocytes that may resemble seminoma cells (19). One pathophysiologic theory suggests that CIS cells are failed gonocytes, thus limited to patients with Y-chromosomal material, like GB (20). CIS occurs almost exclusively in patients with hypovirilization, most notably in AIS. The prevalence of GCT in undervirilized patients is approximately 5–6% in series in which gonadectomy was performed; this should correspond to the incidence of CIS if all such precursor lesions go on to develop malignant lesions (4,18). Partial AIS has been associated with a higher incidence of CIS, however several series have noted the opposite (18). Patients with 46, XY complete dysgenesis DSD should undergo testicular biopsy at puberty to screen for premalignant lesions (1).

Markers

There are several markers under investigation for tumor evaluation in the DSD population beyond beta-human chorionic gonadotropin and alpha-fetoprotein. OCT3/4 (octamer-binding transcription factor) is a well-established pathologic marker for CIS, GB and GCT in adults, but is complicated by expression in developing fetal testes. Given the testicular dysgenesis syndrome hypothesis of developmental delay, this is of particular importance and is thought to contribute to over-diagnosis. However, the expression of OCT3/4 throughout the gonad differs between pre-malignant/malignant cells and developmentally delayed cells (21), which may improve future diagnosis accuracy. Stem cell factor is also used to differentiate malignant from developing germ cells. GB in particular requires the presence of a specific portion of the Y chromosome—the GBY region. The TSPY gene (testis-specific Y-encoded) within the GBY region is expressed in GB (22). Both these lesions—OCT3/4 and TSPY—are also expressed in CIS lesions. Recent studies have demonstrated a possible role for WT1 (Wilms tumor 1) genotyping in 46 XY DSD, including patients with both hypospadias and uni- or bilateral undescended testes. These patients would thus benefit from long-term screening for Wilms tumor, nephropathy and GCT since the mutation was found in 6 of 80 patients with these criteria in one study (23).

Conclusions

The management of patients with DSD is complex and evaluation of tumor risk is aided by advances in genotyping for Y-chromosomal material not evident in traditional karyotyping. More complete genetic screening for DSD patients—indeed even in those with only hypospadias and unilateral undescended testes—should increasingly become the standard of care. Future studies utilizing more advanced histologic examination of gonads to differentiate true malignancy from normal, developing tissue will only help to sharpen our understanding of the true incidences of malignancy in this diverse population.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest

to declare.

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