

Genito-Urinary Malignancies In Patients With Disorders Of Sexual Development: An Experience From A Regional Cancer Center

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Abstract:

Introduction: Disorders of sexual development are a complex group of rare diseases. These disorders are associated with increased risk of other anomalies along with an increased risk of malignancy. We have described three such cases with DSD presenting with genitourinary malignancy.

Case summary: Case 1 is very rare case of ovotesticular DSD with nonseminomatous germ cell tumor underwent surgery followed by chemotherapy. Case 2 is a case diagnosed with persistent mullerian with seminomatous germ cell tumor of the cryptorchid testis. Patient is currently on active surveillance. Case 3 is a case of Wilms tumor with ambiguous genital on pre operative chemotherapy for Wilms tumor.

Discussion: Malformation syndrome associated with DSDs is broadly classified into syndromes associated with defective hormonal and syndromes associated with abnormal morphogenesis. The risk of malignancy is relatively low in patients of ovotesticular DSDs while the risk is quite high in patients of persistent mullerian duct syndrome patient with cryptorchid testis. WT1 gene implicated in the development of genitourinary structures from urogenital ridge when mutated results in DSD along with Wilms tumor.

Conclusion: Patients diagnosed with DSDs need to be monitored closely for the development of malignancies in the later course of life.

I. INTRODUCTION

Disorders of sexual development (DSDs) form a complex entity of heterogeneous etiology that affects the four different dimensions (genetic sex, gonadal sex, phenotypic sex, and behavioral sex) of sexual development. The current nomenclature has replaced the earlier terminologies such as such as intersex, hermaphroditism, and pseudohermaphroditism that are controversial; potentially pejorative to patients; and confusing to the treating physicians (1-3). These disorders often have multiple other malformations associated with genital anomalies and also are associated with increased risk of malignancies either due to the mutated genes having other specific roles in embryogenesis beyond genital development or due to the malignant potential of the dysgenetic gonad that is seen in these patients. In our experience we have come across three such very rare patients with DSDs and associated genitourinary malignancies.

II. CASE SUMMARY

A. CASE 1

A 16 year old male presented to the OPD with complains of rapidly progressing swelling in the lower abdomen and pain in the swelling since one week. Patient was evaluated for the above complains. General examination revealed bilateral gynaecomastia along with penoscrotal hypospadias, microphallus and abdomen examination revealed a suprapubic mass extending up to the umbilicus. Imaging of the abdomen revealed a heterogeneously enhancing lesion in the abdomen along with para aortic lymphadenopathy. Imaging also revealed rudimentary testis like structures in bilateral inguinal canals and also rudimentary uterus like structures. Karyotyping revealed male karyotype 46 XY. Patient was taken up for exploratory laparotomy. Intra operative findings were suggestive of a 12* 15 cm tumor arising from the right ovary along with multiple enlarged lymph nodes. Rudimentary uterus and left ovary were seen. Resection of the tumor and lymph node dissection was done. Post operative histopathology report revealed mixed germ cell tumor comprising of embryonal carcinoma yolk sac tumor and teratoma components. Post operative tumor markers showed elevated α -FP and β HCG are 510 iu/ml and 6166 mIU/ml respectively. Post op imaging revealed no residual disease and patient was planned for 4 cycles of BEP regimen. Patient tolerated chemotherapy well and tumor markers have normalised. Patient is currently on follow up.



Figure 1



Figure 2

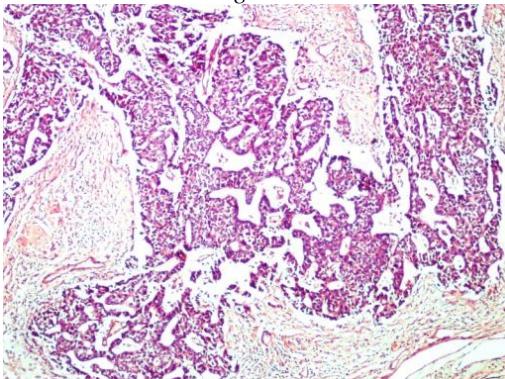


Figure 3

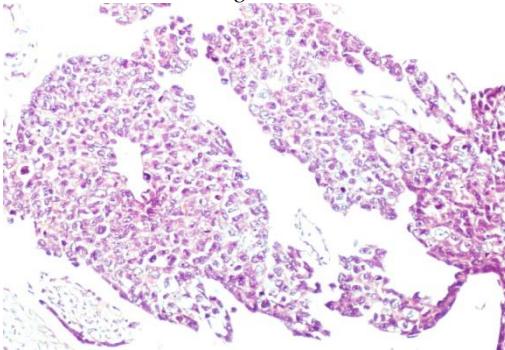


Figure 4

B. CASE 2

Patient a 27 year old male with normal male karyotype 46 XY, presented with a complaints of dragging sensation and pain in the scrotum for which patient was evaluated at a local hospital. On examination an undescended testis was noticed in the right left inguinal region. Patient was taken up for exploratory laparotomy and intra operatively rudimentary uterus with fallopian tubes were seen. Patient underwent a right orchectomy with hysterectomy. Post operative histopathology was suggestive of rudimentary atrophic uterus with right orchectomy specimen showing seminoma in an atrophic cryptorchid testis. Semen analysis was suggestive of aspermia. Sex hormonal analysis revealed elevated levels of serum FSH and LH hormones. The serum testosterone levels were below the normal level. The serum estradiol, growth hormone levels and the thyroid functions are within the normal limits.. Post operative tumor markers were normal and evaluation for regional and distant metastasis was negative. Patient was given options of surveillance, post op radiotherapy and chemotherapy with single agent carboplatin. Patient has opted for surveillance and is currently on regular follow up.

C. CASE 3

A 7 months old preterm baby was accidentally detected with mass per abdomen during feeding. Examination revealed a ballot able 10*8 cm firm mass in the right lumbar region along with penoscrotal hypospadias, micropenis. Abdominal imaging revealed heterogeneous lesions in the upper and lower poles of right kidney and similar lesion in the upper pole of left kidney. Bilateral inguinal hernia with un-descended testis deep to deep inguinal ring was noted. Fine aspiration cytology from kidney revealed Wilms tumor with rhabdomyomatous differentiation. Chest imaging is essentially normal. Urine examination is normal. In view of ambiguous genitalia cytogenetics was performed. Molecular cytogenetics by FISH revealed 46XY in all cells. 17 hydroxy progesterone levels was 0.33 ng/ml well within normal limits ruling out congenital adrenal hyperplasia. Patient is currently on preoperative chemotherapy.



Figure 5



Figure 6

III. DISCUSSION

The terms such as intersex, hermaphroditism, and pseudohermaphroditism have been replaced by term disorders of sex differentiation (DSDs) which is defined as congenital conditions associated with atypical development of chromosomal, gonadal, or anatomical sex. The DSD classification terminology as proposed by the Chicago consensus is being widely used (2,3). Patients presenting with disorder of sex development (DSD) may have other, nongenital malformations associated with DSDs. A review by John M. Hutson et al(5) have classified these malformation syndromes broadly into

- ✓ Defective hormone function (usually androgens) that causes a secondary anomaly of anatomical development
- ✓ Normal hormonal function but aberrant morphogenesis of the internal or external genitalia.
- ✓ Hormonal DSDs are further classified into disorders with
- ✓ Gonadal dysgenesis
- ✓ Hypogonadism
- ✓ Abnormal hormonal function.

In our experience we have had three rare patients with DSD presenting with an associated genitourinary malignancy.

The first patient is a case of ovotesticular DSD with nonseminomatous germ cell tumor arising from ovary. There are very few case reports of mixed germ cell tumors arising from ovary in a case of 46XY DSD with ovotestis. Ovotesticular DSDs previously termed true hermaphrodite present with asymmetrical gonads having both ovarian and testicular elements either separately or in combination. Around 70% of these patients have 46 XX karyotype, 10% have 46XY karyotype while the rest have complex karyotype (7). The risk of malignancy varies from 2.6- 4.6% in these group of patients (4). This is comparatively lower when compare to other DSDs. The most common malignancy in this group of patients is germ cell tumour, histologically dysgerminoma being the commonest. In view of relatively low potential of malignancy in this group of patients prophylactic surgeries are not required. To our knowledge this is the first

case with ovotesticular DSD with nonseminomatous germ cell tumor arising from ovary being reported from India.

The second patient is a case of Persistent Mullerian Duct Syndrome with seminomatous germ cell tumor. This syndrome develops as a result of deficiency of the anti-müllerian hormone or failure of the müllerian ducts to respond to its secretion. Patients are both karyotypically and phenotypically male, but develop both wolffian and müllerian structures such as uterus and fallopian tubes. Neonates present with male external genitalia with normal development of the penis and scrotum, and may have cryptorchidism. One of the proposed hypothesis for cryptorchidism in pmds is a simple passive inhibition of testicular descent by the retained müllerian ducts(5). Testicular tumors are not uncommon in patients with persistent mullerian duct syndrome. The incidence of malignant transformation in these gonads is around 15 %(4). The greater than normal incidence of malignancy is due to the presence of malformed structures, which explains the increased incidence of neoplasia in cryptorchid testes whether or not they are surgically found in the scrotum. These patients are phenotypically normal males; there is a need for preserving the virilization function of the normal testis by primary or staged orchidectomy of the unaffected testis. Testicular malignancy associated with this syndrome requires a staging and treatment policy similar to that for scrotal testicular tumors. Orchidectomy and/or total abdominal hysterectomy should be performed for any tumors found in the testis and/or uterus and fallopian tubes. Removal of the uterus is not necessary, apart from the fact that it is usually difficult to bring the testes down to a normal position.

The third patient is a diagnosed case of Wilms tumor with DSDs. Three syndromes have been well described in the literature establishing the association of Wilms tumor and genital abnormalities i.e. Frasier's syndrome, WAGR syndrome and Denys Drash syndrome (5). All three syndromes have mutations associated with WT1 gene. A number of structures derived from the urogenital ridges, including the gonads and the kidneys, are defective if WT1 contains certain mutations. Mutations in WT1 are thus associated with genitourinary malformations, Wilms tumor, and nephropathy. All three syndromes lead to testicular dysgenesis causing inadequate levels of androgens and partial undervirilization with genital ambiguity. WAGR syndrome is associated with the highest risk of development of Wilms tumor amongst the three syndromes and is also associated with other abnormalities such as aniridia, genitourinary abnormalities, mental and learning disabilities, behavior problems. WAGR syndrome is associated with de novo interstitial deletion of 11p14–11p12, a region that includes WT1 and PAX6. The Denys Drash syndrome consists of a triad of intersex, Wilms's tumour, and nephritic syndrome. Sporadic mutations in the WT1 gene on chromosome 11p13 are responsible for Denys–Drash syndrome. Wilms tumor occurs at an earlier age compared to Frasier's syndrome and is associated with diffuse mesangial sclerosis and risk of gonadoblastoma exists due to presence of streak gonads. The histological features of Wilms's tumour in denys-drash syndrome are no different from the sporadic form, but

intralobar nephrogenic rests are found in the kidneys of most patients with Denys-Drash syndrome. Frasier's syndrome involves a different mutation in WT1 in intron 9 that is usually dominantly inherited. Frasier's syndrome is associated with the least risk of development of Wilms tumor, the risk of gonadoblastoma is very high. Focal segmental glomerulosclerosis is the cause of nephropathy in this syndrome.

IV. CONCLUSION

Disorders of sexual development are a set of very rare malformations arising due to diverse etiological factors. The life time risk of development of malignancies, predominantly germ cell tumors increases with the age of the patient. We have brought forth three such very rare patients with DSDs and genitourinary malignancies. Due to the mutations in genes such as WT1, associated with the development of various structures urogenital ridge genitourinary malignancies and Wilms tumor co exists. While abnormal sex hormonal levels leading to altered secondary sexual characters that may be associated with crypto-orchidism increases the risk of germ cell tumors. Thus patients diagnosed with DSDs need to be monitored closely for the development of malignancies in the later course of life.

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