

CASE REPORT

COMPLETE ANDROGEN INSENSITIVITY SYNDROME WITH MIXED GERM CELL TUMOR – CASE REPORT

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ABSTRACT: Testicular feminization syndrome or androgen insensitivity syndrome is a rare inherited form of male pseudohermaphroditism that occurs in phenotypically normal woman with male karyotype (XY), with an incidence of 1:20,000-64,000 male births. The individual with complete form of this syndrome have female external genitalia while those with partial form have variable ambiguity of genitalia. The undescended testis may go into malignant transformation. The androgen insensitivity syndrome with malignant testicular disorder is very rare. A twenty-eight year old female was admitted to the hospital with the complaint of primary amenorrhea. Clinical and laboratory investigation revealed testicular feminization syndrome with seminoma developed from intraabdominal undescended testis. Primary removal of the mass and postoperative chemotherapy was treatment of choice for the patient.

KEY WORDS: Testicular feminization syndrome, Germ cell tumor, Seminoma.

INTRODUCTION: Androgen insensitivity (testicular feminization) syndrome is a rare inherited form of male pseudohermaphroditism that occurs in phenotypically normal woman with adequate breast development, normal external genitalia, a vagina of variable depth, absent uterus, and sparse or absent pubic hair and axillary hair. These patients have male karyotype (XY) and negative sex chromatin. The gonad (undescended testes) may be intra abdominal, inguinal, or labial. It is a relatively rare syndrome with the association of malignancy even more rare (1). This paper is a case presentation of a young woman with seminoma arising in testicular feminization syndrome.

CASE PRESENTATION: A 28 years old female with primary amenorrhoea with married life of 8 yrs reported on 5.9.2011 with complaint of abdominal pain and lump abdomen. She has one aunt and 6 sisters and all have normal menstrual functions. On examination, she had normal breast development with scanty axillary and pubic hair (Tanner Stage - II). There was a tender, mobile mass with smooth borders in the suprapubic region reaching upto umbilicus. On pervaginal examination there was a 3 cm blind vagina. USG (29.8.11) showed a very large complex (solid cystic) mass in pelvis with increased vascularity and calcification. Uterus or ovaries were not visualized separately. Multiple pre and para aortic lymph nodes were enlarged and encasing the aorta forming a large retroperitoneal mass pushing the right kidney. Another heterogeneous mass of same echotexture as the pelvic mass was seen at lower pole of right kidney obstructing ureter. No ascites was present. The findings were corroborated on CT (31.8.11) (Fig.2) scan abdomen which showed a large heterogeneous solid mass in pelvis and lower abdomen of size 22 x 12 x 15 cm with cystic areas and multiple small intralesional vessels compressing urinary bladder and rectum. Uterus and

CASE REPORT

ovary were not seen separately. A similar mass of size 15 x 17 cm encasing the aorta and B/L renal vessels was seen in retroperitoneum, likely nodal mass.

Serum levels of LDH, hCG and AFP were found to be 1970 U/L (160-420 U/L), 275 mIU/ml (<5.30 mIU/ml) and >300 IU/ml (0.5-5.5 IU/ml) respectively. While the levels of CA-125-16.8u/ml (upto 21u/ml normal), CEA 1.72ng/ml (upto 2.4=normal), S.17 hydroxy progesterone 0.68ng/ml (0.3-2.3ng/ml) and serum testosterone <20ng/dl were within normal range. S.DHEAS was 60.2microgm/dl (167.9-591.9). On karyotyping (Fig. 1), (GTG-Banding with 500 band resolution) chromosomal study revealed male karyotype in all cells analyzed. Hence, a diagnosis of complete androgen insensitivity syndrome with germ cell tumor with retroperitoneal lymph node metastasis was made.

Staging laparotomy was performed. A 22 x 15 x 14 cm regular gonadal mass on right side and 5 x 2 x 1.3 cm left gonad were surgically removed. A large mass of about 15 x 17 cm was encasing the aorta from which only 3.5 x 2 x 1.5 cm mass could be removed (Fig.3). Partial omentectomy was done. Uterus and tubes were not visualised. Peritoneal washings were negative for malignancy. Histopathology revealed - mixed germ cell tumor, predominantly seminoma with focal areas of yolk sac tumor in the right gonad while the left gonad showed testicular tissue comprising seminiferous tubules with arrest in spermatogenesis and leydig cell hyperplasia. Paraaortic lymph node showed metastasis by mixed germ cell tumor while the omentum showed no evidence of metastasis. Chemotherapy - BEP regime, 4 cycles, were planned, (Bleomycin - Etoposide - Cisplatin). Chemotherapy was given and finished in January 2012.

The treatment was completed satisfactorily after which her serum levels of LDH, hCG and AFP were 190 U/L, 4.10mIU/ml and 4.5 IU/ml respectively. Follow-up CT scan (14.6.12) showed no paraaortic mass.



Fig.1 A chromosomal study showing male karyotype

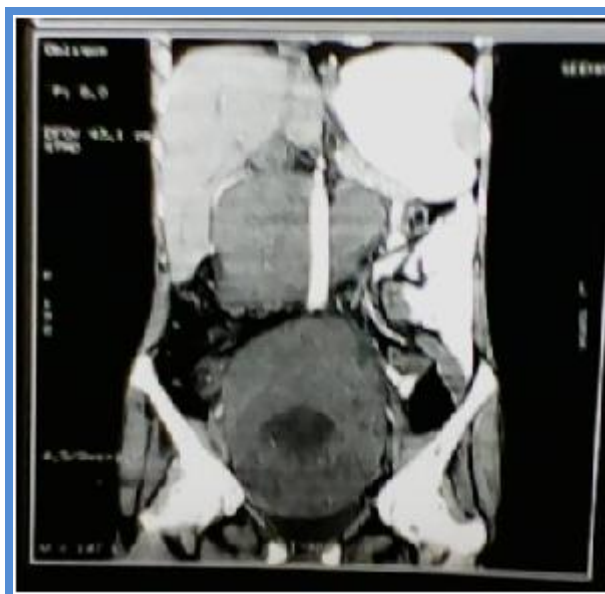


Fig.2 CT Scan showing large heterogeneous solid mass in pelvis. A similar mass encasing the aorta and B/L renal vessels

CASE REPORT

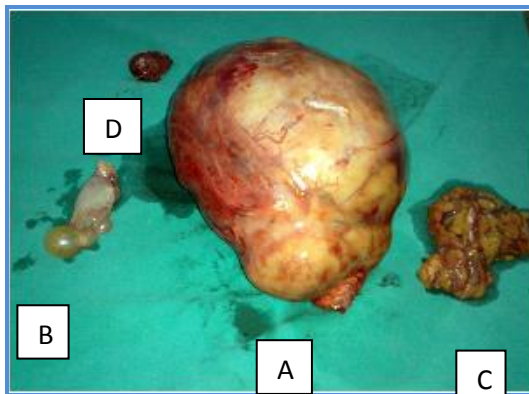


Fig.3 Showing Right Gonadal mass (A) Left Gonad (B) Omentum(C) Para Aortic lymph node (D)

DISCUSSION: Complete Androgen insensitivity syndrome (CAIS) was initially described in 1953 and has an incidence of 1: 2000 to 1: 64,000(2) and accounts for 10% of cases of primary amenorrhoea (3).They present either with inguinal hernias, or labial masses, primary amenorrhoea during adolescence, primary infertility after marriage. A diagnosis of CAIS can be made in cases of primary amenorrhoea with normal breast development, absent or scanty pubic and axillary hair, a short vagina and an absent cervix and uterus, a serum testosterone in the normal male range and with 46 XY karyotype.

Androgen insensitivity syndrome (AIS) results from an androgen receptor defect (4). The probable explanation of the syndrome is the absence of the cytosol androgen binding protein receptor that is normally present in the androgen responsive tissue. So, the male fetus is not stimulated by normal levels of circulating androgens. As a result, there is no fusion of the genital folds to form scrotum and penis and no posterior migration of the labioscrotal folds (5).CAIS can result from a wide variety of inactivating mutations in the AR gene. It follows X-linked recessive pattern of inheritance so, careful investigations to identify other affected family members is warranted. Approximately 40% patients with complete AIS have no family history, representing de-novo mutation. The diversity of AR mutations may be related to diversity in phenotype (6).

Testicular feminization syndrome may present as complete form (CAIS) and incomplete form (PAIS) (2). In the complete form, there is no androgen response, therefore normal external female genitalia develop and these infants are reared as females. There may be labial or inguinal swellings which contain testis. These patients most often present in late adolescence with primary amenorrhoea. There is absence of uterus and ovaries on ultrasound scan or laparoscopy. Vagina is short, develops from urogenital sinus only and ends blindly. The partial or incomplete form of testicular feminization syndrome is associated with wide range of genital abnormalities and typically present at birth with genital ambiguity (3). Ultrasonography or laparoscopy should be done in all such patients to examine internal genital organs. Measurement of serum 17-hydroxyprogesterone and its sulphate can be done to detect testosterone biosynthetic defects (2). Management consist of appropriate counseling of parents regarding fertility and long term use of HRT needs to be discussed. Reconstructive surgery to external genitalia is not needed in the complete form but gonads need to be removed due to risk of malignancy.

In patients with CAIS, gonadectomy generally is best delayed until after puberty is completed as pubertal development generally proceeds more smoothly in response to endogenous hormonal

CASE REPORT

production(7) and the overall risk for tumor development is 5-10% especially below puberty. However CAIS has been diagnosed in testicular biopsies in prepubertal patients so routine USG examination of gonads can be used to monitor potential malignant changes.

The risk of malignancy in AIS is considerably lower and occurs at a lower age than with other inter-sex disorders. Most common malignancy in these cases has been found to be seminoma. Depending upto the malignant spread, adjuvant therapy is warranted.

CONCLUSION: Complete AIS results from a wide variety of inactivating mutations in AR gene located on X chromosome (Xq12). Clinical management of complete AIS includes appropriate hormone therapy, creation of a functional vagina, gonadectomy to prevent tumorigenesis in cryptorchid testis and psychological support. The overall risk for tumor development in cryptorchid gonads is 5-10%.

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