Bilateral Gonadoblastomas with a Left Sided Dysgerminoma in a True Hermaphrodite (Disorder of Sexual Differentiation) with 46, XY Karyotype

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Abstract
Ovotesticular DSD is not an uncommon disorder. The presence of Y chromosome confers a high risk of neoplastic transformation in dysgenetic gonads. The neoplastic development in these patients is associated with the presence of Y chromosome and intra abdominal location of the abnormal gonad. We report histogenetic details of a rare occurrence of bilateral gonadoblastomas and left sided dysgerminoma in a XY ovotestes DSD (disorder of sexual differentiation) in an 18 year old with a female phenotype. ©

INTRODUCTION

The increased malignant potential of abnormal gonads in patients harbouring a Y chromosome is well recognised. The presence of this Y chromosome confers a high risk of neoplastic transformation in dysgenetic gonads. At 25 years of age, the estimated rate of tumour formation in intersex patients with a Y chromosome is 75%. Gonadoblastomas and dysgerminomas are the most commonly encountered tumours in this subset of patients. We report the case of a true hermaphrodite with a 46,XY karyotype and bilateral ovotestes, who was found to have bilateral gonadoblastomas and a left sided dysgerminoma.

CASE REPORT

An 18-year-old girl presented with primary amenorrhoea. On examination, she had hirsuitism on the face, breasts and abdomen with the Ferriman-Gallway score of >12/36. Her secondary sexual characters were normal but for minimal clitorimegaly (1.2 cms). She weighed 56 kilograms and her height was 168 centimetres. The rest of physical examination was unremarkable. There was no family history of a similar complaint.

An ultrasound examination of the pelvis showed a hypoplastic uterus with bilateral streak gonads. The haemogram, blood urea, serum creatinine and thyroid function tests were normal. Her leutinizing and follicle stimulating hormone (LH and FSH) levels were 38.5 mIU/l (normal 2-15 mIU/l) and 64.7 mIU/l (normal 3-20 mIU/l) respectively. The serum oestradiol was 42.9 pg/ml (normal 0-160 pg/ml) Serum testosterone was 3.78 ng/ml (normal 0.4-1.02 ng/ml) while dehydroepiandrosterone sulphate was 362 µg/dl (normal 35-140). In view of the presence of streak gonads in this patient with a female phenotype and hypergonadotropic hypogonadism, a tentative diagnosis of a Mosaic Turner syndrome was made. These features in a patient less than 30 years of age with no ambigious genitalia necessitated karyotyping which showed a 46 XY karyotype. At this juncture, a XY Pure gonadal dysgenesis needed to be considered in the differential diagnosis. As secondary sex characteristics were well developed in this patient, a possibility of a gonadal tumour capable of producing oestrogens needed to be considered in addition. In view of the XY genotype and dysgenetic gonad which is associated with high risk of malignancy, a prophylactic laparoscopic gonadectomy was carried out. Per-operatively, the left gonad had the appearance of an ovary, while, the right one was noted to be a streak gonad. Both gonads were excised and subjected for histopathologic examination which showed features of ovotestes bilaterally establishing the final diagnosis of true hermaphroditism along with a neoplasm composed of a biphasic population of germ cells and sex cord cells. The germ cells in addition showed cell groups which were hyperchromatic and pleomorphic with focal associated granulomatous response. Leydig cells were also noted. There was evidence of haemorrhage and foci of luminal calcification (Figs. 1A, 1B). These features seen in both the gonads were diagnostic of gonadoblastoma. In addition, the left gonad showed features of a classical dysgerminoma which accounted approximately 38% of the specimen (Fig. 2). The latter was characterised by nests

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Received : 10.9.2007; Revised : 8.2.2008; Re-Revised : 10.4.2008; Accepted : 20.5.2008
and trabeculae of large uniform round to oval cells with slightly granular or clear cytoplasm and round or oval nucleus. The connective tissue stroma showed an infiltrate of lymphocytes. No primitive/embryonal cell component was identified and this correlated well with negative α-fetoprotein and hCG levels in serum.

**DISCUSSION**

Ovotesticular disorder of sexual differentiation (DSD), previously known as true hermaphroditism is the rarest of the intersex disorders and is characterised by the presence of both ovarian and testicular tissue either in the same or opposite gonads. The rarity may be because most of the fetuses do not survive the rigors of intrauterine environment as explained by Lee. When the disorder is compatible with life, around 94% of cases are diagnosed during the first three decades.

The diagnosis of DSD should be considered in all patients with ambiguous genitalia. The abnormal appearance of the external genitalia is the most frequent presenting symptom. The differentiation of the genital tract and development of secondary sex characteristics are very variable. Production of oestrogen by the ovarian tissue results in the development of a female phenotype with development of female secondary sexual characters. A normal or almost normal male appearance with penile hypospadias or small penis is also reported. Cryptorchidism is common, but at least one gonad is palpable usually in the labioscrotal fold or more often in the inguinal region as an inguinal hernia. Rarely, clitorimegaly may be present at birth or develop at puberty. Secretion of androgens by “Leydig cells” in the gonadal streak is a possible cause, as is the presence of cryptic Y cell line.

The differentiation of the genital ducts in DSD is often seen as a hemiuterus or rudimentary uterus on the side of the ovary or ovotestis. The ovotestis is the most frequent gonad found (59%), the two components being arranged end to end. According to the nature and location of the gonadal tissue, ovotestis could be either lateral (20%) when testis is on one side and ovary on the other and bilateral (30%) when ovotestis is present on both sides. Unilateral cases (50%) have an ovotestis present on one side and an ovary or testis on the other.

The karyotyping in approximately 60% of patients reveals a 46 XX karyotype; 10% show a 46 XY karyotype and the remainder is characterized by various forms of mosaicism XX/XY. In a true hermaphrodite with a 46 XY karyotype, the testicular element is usually dysgenetic and hence the risk of malignancy is 28% by the age of 20 years while for patients with mixed gonadal dysgenesis, it is 19% at the same age. According to Alonso et al, TPSY gene (testis-specific protein, Y encoded) localised within the GBY locus (gonadoblastoma locus on the Y chromosome) participates in the multistep malignant transformation.

Gonadoblastomas (also known as dysgenetic gonadomas), an unusual mixed germ cell-sex cord-stromal tumour which has the potential for malignant transformation affects a subset of patients with intersex disorders. They may undergo complete regression by process of hyalinisation and calcification (80%) and 30% of them may progress to either dysgerminoma/ seminoma. An additional 10% of gonadoblastomas develop various types of germ cell neoplasms such as yolk sac tumour, immature teratoma, embryonal carcinoma, and choriocarcinoma. Thus, the presence of gonadoblastoma in young patients with DSD and their potential risk for malignant transformation calls for early diagnosis and treatment requiring prophylactic removal of gonads in these cases.

This case study, thus, reiterates the malignant potential of dysgenetic gonads in the presence of a Y chromosome and reconfirms that tumours could often be present in dysgenetic gonads requiring prophylactic removal of the gonads. Oestrogen secreted by the gonadal tissue or
by one/both of the gonadoblastomas is the most likely explanation for the development of female secondary sexual characteristics in our patient. In a similar way, androgen secretion by the tumour or the testicular element may have resulted in hirsuitism and clitoromegaly. However, the elevated levels of gonadotrophins despite the detection of both oestrogen and testosterone in the serum is an unaccountable biochemical feature in this patient.

REFERENCES


Announcement

6th National Conference of Cardiology, Diabetology, Electrocardiology, Echocardiography and Critical Care. 7th and 9th November 2008 at Hotel Jehan Numa Palace, Shamla Hills, Bhopal (M.P)

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