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Testicular germ cell tumor in a female patient with male pseudohermaphroditism - a rare case report

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Abstract :
Testicular germ cell tumors in patients with disorders of gonadal development have been reported in literature. A 38 year old phenotypically female patient with primary amenorrhoea came to our hospital with complaints of an inguinoscrotal mass and was subsequently diagnosed to have male pseudohermaphroditism, possibly testicular feminisation syndrome. Clinical and laboratory investigations suggested the diagnosis of a germ cell tumor of the testis. The patient underwent high inguinal orchiectomy followed by post operative chemotherapy. The post operative diagnosis was mixed germ cell tumor of the testis in a male pseudohermaphrodite. The association is notable for its rarity.
Keyword :testicular germ cell tumors, pseudohermaphroditism, testicular feminisation

Introduction:

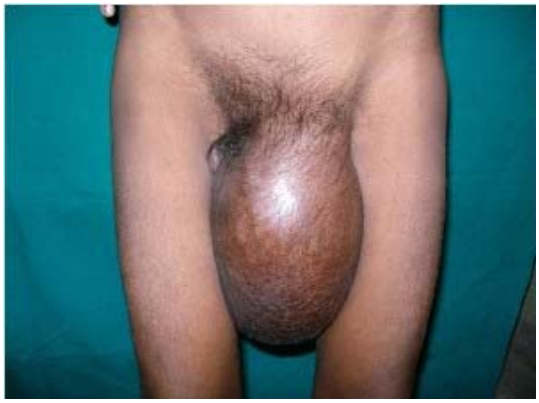
Testicular germ cell tumors are relatively uncommon with an excellent outcome. A variety of predisposing factors have been identified for these tumors and mainly include cryptorchidism, chromosomal aberrations and disorders of gonadal development (hermaphroditism). Hermaphroditism is an uncommon condition of gonadal development where there is a mismatch between the genetic sex and the phenotypic sex. These patients have a marked predisposition to development of a variety of malignancies which includes germ cell tumors. Such cases are very rare and only a few hundred cases have been reported in literature.

Case presentation:

Our patient was a 38 year old phenotypically female patient with an eight year history of a swelling in the ilioinguinal region, for which she had never sought medical attention. She had been raised as a female and there was a history of a primary amenorrhoea. Apart from occasional pain, she did not have any symptoms pertaining to the swelling except that it was gradually increasing in size over the past eight years. On examination, she was phenotypically female, with sparse axillary and pubic hair

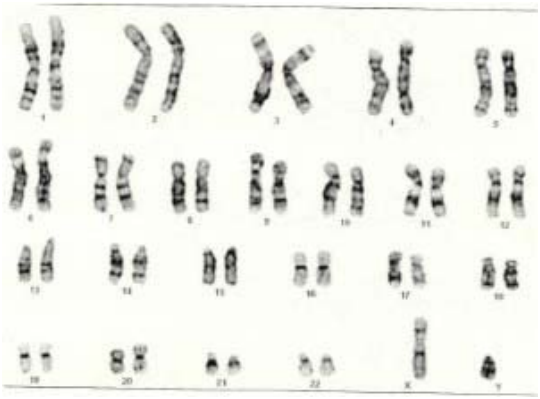
and developed breasts. There was a 23x17x8 cm lesion in the left inguinal region which was firm and non tender. There was a hypertrophied clitoris, blind vagina and ill developed labia majora. The urethra was in normal position.

PHENOTYPICALLY FEMALE:



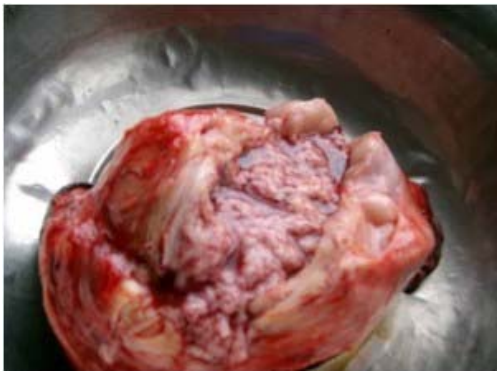
A CT scan of the abdomen showed a heterodense soft tissue density in the inguinoscrotal region with evidence of fluid in a doubtful scrotal sac. Uterus and ovaries were not visualised. There was no evidence of any lymphadenopathy or ascites. Chest imaging was normal. The patient had elevated serum Lactate dehydrogenase (2860 IU/L). The serum human chorionic gonadotropin was marginally elevated (30.3 mIU/ml) and serum fetoprotein was normal (3.8 IU/ml). Fine needle aspiration cytology of the tumor was suggestive of malignant germ cell tumor, seminoma. A karyotyping was done which revealed a normal male 46 XY karyotype without any structural aberrations. Family history was unremarkable. A clinical diagnosis of testicular germ cell tumor in a male pseudohermaphrodite (possibly androgen insensitivity syndrome) was made.

inguinoscrotal mass normal male karyotype 46 XY:



The patient subsequently underwent a left sided high inguinal orchiectomy. The gross specimen measured 23x16x7 cm and appeared grey white with areas of nodularity. The tumor was encapsulated with capsule peeled off in some areas. There was marked necrosis on cut section with multiple cystic areas, largest measuring 2 cm. One pole showed a fibrofatty cord like structure measuring 3 cm.Microscopic sections showed the presence of a mixed germ cell tumor with a predominant seminomatous component (95%) and a minor yolk sac component.

There were extensive areas of necrosis. Spermatic cord showed invasion by the same tumor. There was no lymphovascular invasion. The final stage was designated as pT3N0M0 according to the AJCC 7th edition TNM staging [1]. The patient received four cycles of standard BEP chemotherapy (bleomycin + cisplatin + etoposide) once in 21 days. On re-



evaluation, there was no evidence of disease and marker levels were normal. The patient is doing well and on regular follow up with our department according to the follow up schedule for testicular germ cell tumors.

MASS REMOVED IN TOTO:

Discussion:

Disorders of sexual differentiation occur approximately between 1 in 3000 and 1 in 7000 newborns. Intersex disorders include conditions with discordance between chromosomal sex and gonadal sex of the individuals. The spectrum broadly includes pseudohermaphroditism and true hermaphroditism. True hermaphrodites by definition have both ovarian and testicular tissue in the gonads which may occur separately or together as ovotestes whereas pseudohermaphrodites possess only one type of gonad with opposing phenotype which may be male or female [2].Male pseudohermaphroditism is inherited as a sex-linked recessive disorder. The spectrum ranges from the mild cases with hypospadias, cleft scrotum and undescended testes, to the more hermaphroditism. True hermaphrodites by definition have both ovarian and testicular tissue in the gonads which may occur separately or together as ovotestes whereas pseudohermaphrodites possess only one type of gonad with opposing phenotype which may be male or female [2].

Male pseudohermaphroditism is inherited as a sex-linked recessive disorder. The spectrum ranges from the mild cases with hypospadias, cleft scrotum and undescended testes, to the more severe forms of testicular agenesis (Turner's syndrome), or dysgenesis (testicular feminization syndrome). Testicular feminisation is one of the most common forms of male pseudo-hermaphroditism. Testicular dysgenesis leads to inhibition of spermatogenesis and a Sertoli cell dominant state (“feminizing” testis), also known as an androgen insensitivity syndrome (AIS) [3].

These patients, despite having a male genotype present as asymptomatic, functionally normal but reproductively sterile females. The testis is often undescended and the ovaries, uterus, fallopian tubes, and upper third of the vagina are typically absent. Externally, the labia majora and minora are usually well formed. AIS is caused by mutations in the androgen receptor gene and is associated with abnormal testicular development [4]. Such patients have an increased susceptibility to malignancy such as carcinoma of the breast, Sertoli adenoma, germinoma in situ and seminoma.Overall prevalence of germ cell tumors in patients with intersex disorders is around 30% (most common in gonadal dysgensis). Malignancy occurs at a younger age in patients with dysgenetic gonads

than in patients with other intersex syndromes. Gonadoblastoma is the most common tumor in a dysgenetic gonad, although seminoma-dysgerminoma can occur. Gonadoblastoma is considered to be the precursor of type II germ cell tumors which occur in these patients [5]. The other malignancy which is common in XY gonadal dysgenesis is Wilm's tumor especially in association with the Drash syndrome and screening has been recommended for such patients. There has also been a recent classification suggested for patients with disorders of virilisation and gonadal dysgenesis based on the potential for subsequent malignancy. Reasons quoted for increased neoplastic potential in patients with intersex syndromes include presence of XY gonadal tissue in an inappropriate milieu and genetic process which by itself resulted in the dysgenetic gonad. In complete testicular feminisation, the risk of malignancy increases exponentially with age, especially after the 3rd decade [5].One of the earliest published reports of malignancy occurring in a pseudohermaphrodite were in 1960 by Teter et al who reported a case of gonadoblastoma in a patient with testicular dysgenesis[6]. Subsequently there have been many case reports of malignant transformation in patients with androgen insensitivity syndrome. Goel et al reported a case of bilateral seminoma in a patient with male pseudohermaphroditism[7]. Whitehead et al reported a case of cryptorchid seminoma presenting as inguinal hernia in a patient with testicular feminisation [8]. Darshana D. Rasalkar et al [9] and Zorlu et al [10] have reported cases of intra-abdominal testicular seminoma in a woman with testicular feminization syndrome. Mixed germ cell tumor has been reported in a male pseudohermaphrodite by Heng Zhang et al [11]

The identification of neoplasia in patients with testicular feminisation has led to many studies which have emphasised on the early identification and prevention of malignancy in these patients. In a study by Morris and Mahesh, a 22% incidence of malignant gonadal tumors was seen in a series of 181 patients with AIS. Most of the patients in this series were in the third decade and majority had germ cell tumors [12]. Our patient was also in the late third decade at the time of diagnosis. Review of literature suggests that the risk of malignancy is quite low in AIS in the early years of life but substantially increases with age most patients being diagnosed in the 3rd and 4th decades. There are other case series which have found very little association with between malignancy and AIS. In a review by Dewhurst et al, no malignancy was seen in 82 patients with this syndrome. The estimated chance of malignancy in AIS according to this series was approximately 5% [13]. Manuel et al. reported a series of 23 cases of AIS and concluded that the risk of malignancy is 3.6% at age 25 and 33% at age 50 [14].Since there is a relatively low incidence of malignancy in these patients, some authors believe in allowing for natural puberty to occur before considering gonadectomy. There have been studies to find out if testicular biopsy could accurately predict the premalignant changes in these patients. Muller et al performed gonadal biopsy in 12 patients with AIS and found intratubular neoplasia in three patients. On subsequent follow up, three of the 12 patients developed carcinoma in situ. These authors concluded that a testicular biopsy is warranted as soon as the patient is diagnosed with AIS and mandates an

orchiectomy if preneoplastic changes are present [15].Our patient was a male pseudohermaphrodite and probably comes under the syndrome of testicular feminisation. The patient had been raised as a female due to the presence of a female phenotype. Testicular feminisation is usually diagnosed by the 2nd or early 3rd decade since the patients present with primary amenorrhoea. Although it is rarely diagnosed beyond the 3rd decade, delayed presentations of intersex disorders are common in our country probably due to lack of education and this increases the chance of malignancy due to delayed diagnosis. The social enigma behind the intersex disorders prevents these patients from obtaining any form of medical assistance. Management of a germ cell tumor in patients with these disorders is same as those occurring in individuals without the disorder. Considerations should be given for prophylactic orchiectomy in these patients. Many authors feel that at least one gonad should be left behind for puberty to occur, considering the fact that malignancy is quite uncommon in these patients before puberty. Orchiectomy soon after puberty has been recommended for several reasons, the most important one being prevention of an anticipatedmalignancy. The other reasons include definition of a phenotypic sex for these patients for social reasons, which is very important in a country like ours and also for correction of certain other immunological and neurological disorders occurring in these patients [16, 17].

References:

1.AJCC TNM cancer staging manual, 7th edition, 2009

2 J. L. Rutgers and R. E. Scully, “The androgen insensitivity syndrome (testicular feminization) a clinicopathologic study of 43 cases,” International Journal of Gynecological Pathology, vol. 10, no. 2, pp. 126–144, 1991.

3 Griffin J, Wilson J. The syndrome of androgen resistance. N Engl J Med 1980;302:198-209

4 C. B. Coulam, M. L. Graham II, and T. C. Spelsberg, “Androgen insensitivity syndrome: gonadal androgen receptor activity,” American Journal of Obstetrics and Gynecology, vol. 150, no. 5, part 1, pp. 531 –533, 1984.

5 Verp MS, Simpson JL. Abnormal sexual differentiation and neoplasia: Cancer Genet Cytogent 1987 Apr; 25(2):191-218.

6 Jerzy Teter. An Unusual Gonadal Tumour (Gonadoblastoma) in a Male Pseudohermaphrodite withT-esticular Dysgenesis: BJOG: An International Journal of Obstetrics & Gynaecology Volume 67,Issue 2 pages 238–242, April 19607.

7 Goel RG, Samuel KC. Bilateral seminoma in a male pseudohermaphrodite:J Urol . 1972 Sep; 108 (3):466-8.

8 Whitehead S, Guthrie J, Karran SJ. Malignancy in an internal male pseudohermaphrodite.Cryptorchid testis with seminoma presenting as inguinal hernia: J R Coll Surg Edinb 1984 Mar;29(2):123-5.

9 Darshana D. Rasalkar, Bhawan K. Paunipagar, Alex Ng, Fernand M. Lai, and Shalini Jain Bagaria. Intra-Abdominal Testicular Seminoma in a

10 Faruk Zorlu, Mustafa Cengiz, Murat Gürkaynak, Ferah Yildiz, I. Lale Atahan. Seminoma Arising InAndrogen Insensitivity Syndrome (Testicular Feminization Syndrome): A Case Report: TurkishJournal of Cancer, Vol.31/ No. 4/2001.

11 Morris J, Mahesh V. Further obser vations on the syndrome, "testicular feminization." Am J Obstet Gynecol 1963; 87:731-3.

12 Zhang Heng, Liu Li-mei, Duan Guang-jie, Yao Hong, Chen Tu-nan, Lu Gen-sheng. Male pseudohermaphroditism with mixed germ cell tumor: Pediatric Blood & Cancer Volume 56, Issue 5,pages 873–874, May 2011

13 Dewhurst CJ, Ferreire HP, Gillet PG. Gonadal malignancy in XY females. J Obstet Gynaecol BrCommonw 1971; 78:1077-83.

14 Manuel M, Katayama KP, Jones Jr HW. The age of occurrence of gonadal tumors in intersex patients with Y chromosome. Am J Obstet Gynecol.1976;124:293-300

15 Muller J, Skakkebaek N. Testicular carcinoma in situ in children with the androgen insensitivity (testicular feminization) syndrome. Br Med J1984; 288:1419-20.

16 Z. Hrabovszky and J. M. Hutson, “Surgical treatment of intersex abnormalities: a review,” Surgery, vol. 131, no. 1, pp. 92–104, 2002

17 Portuondo JA, Neyro JL, Barral A, et al. Management of phenotypic female patients with an XYkaryotype. J Reprod Med 1986; 31:611-5.