CASE REPORT

A case reported with 46, XX testicular disorders of sexual development and its possible association with dysembryoplastic neuroepithelial tumour

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Abstract

The main factor determining differentiation of bipotential gonads into testes or ovaries is the presence or absence of SRY (sex-determining region on Y chromosome) gene. De la Chapelle syndrome is a chromosomal anomaly with chromosomal makeup of a female (46, XX) and phenotypic presentation of a male. Previously known as XX sex reversal, it is now called 46, XX testicular disorders of sexual development (DSD). Although rare, it presents as a major chromosomal anomaly, with SRY gene crossover proposed as an underlying aetiology in most patients.

We report the case of a 25-year-old male who presented with infertility and was diagnosed with De 46, XX testicular DSD. He has a previous history of resected dysembryoplastic neuroepithelial tumour (DNT). The differential diagnosis of 46, XX DSD and possible association/coincidental finding of DNT have been discussed. Karyotyping should be a part of the workup for every patient who presents with infertility and has azoospermia and hypergonadotropic hypogonadism.

Keywords: SRY gene, XX sex reversal, testicular disorder of sexual differentiation (DSDs), dysembryoplastic neuroepithelial tumour (DNT).

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Introduction

The 46, XX Testicular Disorders of sexual differentiation (DSD) is a rare anomaly with the characteristics of discordant chromosomal and gonadal sex.[1] Individuals with classical 46, XX testicular DSDs have an apparently normal male phenotype. The usual presentation is infertility because of azoospermia and/or a combination of gynaecomastia, hypospadias, and cryptorchidism depending on the presence or absence of the SRY (sex determining region Y) gene.[2]

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This syndrome remains a rare clinical entity with only about 100 cases reported in the medical literature so far. It is particularly hard to diagnose because it's very rarely seen, and because there are not any specific clinical characteristics that are present in 46, XX DSD patients, as opposed to Down's syndrome for instance. Therefore, in patients presenting with infertility, the possibility of this syndrome should be kept in mind besides the usual infertility workup and karyotyping should be considered for evaluation of azoospermia with hypergonadotropic hypogonadism.

The clinical presentation varies from ambiguous genitalia to completely normal male external genitalia.[3] Literature on endocrinological and neurological presentation of testicular DSD is scarce. Through this case we highlight its clinical, genetic and endocrinological features, the possible differential diagnosis, and discuss any possible association it might have with dysembryoplastic neuroepithelial tumour (DNT).

Case Report

On May 2012, a 25-year-old male, married for two years, presented to the endocrine clinic at Aga Khan University Hospital (AKUH) Karachi for evaluation of primary infertility. There was no parental consanguinity and he was born at term after an uneventful pregnancy. Childhood development was normal. He had a history of resection of an intracranial mass, at 14 years of age which was diagnosed after brain imaging was done for intractable seizures. After surgery his anti-epileptics were stopped, and he remained well with no further episodes of seizures or any other complications. Histopathology of the intracranial mass revealed dysembryoplastic neuroepithelioma.

He has two brothers and one sister, all of whom are healthy. There is no family history of infertility, seizures, or tumours. He is an intelligent and well-educated person. According to the history, he shaves daily and has normal morning erections and libido. Frequency of intercourse with his wife averages thrice weekly.

On examination, Body Mass Index (BMI) was 22kg/m^2 (normal range for Asians 18.5-22.9)[4] and arm span of 173cm with unremarkable general and systemic

examination. He had normal facial, axillary, and pubic hair growth. He had normal male external genitalia with no gynaecomastia. The stretched penile length was 7cm with normal width and both testes were of normal volume (15ml) and palpable bilaterally in the scrotum. Palpation of inguinal region did not reveal any abnormal structures and the urethral opening was normal, i.e. there was no hypospadias.

During his workup for infertility, semen analysis showed azoospermia with low ejaculatory volume (1cc) and the hormonal profile showed elevated follicle-stimulating hormone (FSH) 29 mIU/ml (normal range 1.5–15.0mlU/ml), while the serum concentration of the total testosterone and the Anti-Mullerian (AMH) hormones were low at 3nmol/l (normal range 8.3–38.2mlU/ml) and 0.19ng/ml (normal range 2.0–5 ng/ml), respectively. The luteinizing hormone (LH) was 6mlU/ml (normal range is 1.4–7.7mlU/ml). Thyroid function tests and serum prolactin level were normal, which though are not required for the evaluation of hypergonadotropic hypogonadism. An ultrasound of the pelvis showed no evidence of uterus or ovaries and showed a normal sized prostate gland. Chromosomal analysis showed a 46, XX karyotype. The presence of SRY gene on X chromosome of this patient should have been documented through FISH analysis but, unfortunately, this test is not available in Pakistan.

Discussion

The 46, XX testicular DSD was first described by De la Chapelle in 1964[1,5] and since then it has been known with multiple names, i.e. De la Chapelle syndrome, 46, XX sex reversal syndrome, XX male syndrome or XX sex reversal.[5] In 2005, an international consensus meeting on intersex was held in Chicago where a new nomenclature was proposed. According to this nomenclature, XX sex reversal was placed under the term 46, XX testicular DSDs.[1, 6] It is a rare condition reported in 1 in 20,000 males.[1] Most of the reported cases were sporadic with no positive family history but a few of them were familial as well. Our patient will be considered a sporadic case of testicular DSD as his family history was negative for such disorder.

Human sexual development can be divided into two phases, the first phase being determined by the SRY gene coding for gonad formation resulting in sex determination while the second phase is characterised by somatic cells differentiating into gonads.[7] Thus, the presence of SRY gene is considered crucial for sex discrimination and based on the presence and absence of SRY gene, XX testicular DSD can be classified into two broad groups: SRY positive and SRY negative.[8] This classification is important because both the groups have some differences in clinical presentation.

Most of SRY positive patients present later in life with fertility problems (azoospermia) with normal or under developed testes and in some cases may have cryptorchidism but signs of masculinity are present in most of these cases.[8] Majority of 46, XX DSDs are SRY positive, i.e. 80%, and around 2% of male infertility is because of this syndrome.[9] The main mechanism for this disorder is the transfer of a portion of Y chromosome containing SRY gene to the short arm of X chromosome during paternal meiosis resulting in XX genotype with SRY gene.[3] So, the gonads differentiate into testes and male phenotype develops under the influence of this SRY gene, but the sperm production is impaired due to the absence of azoospermia factor gene (AZF) found on the long arm of Y chromosome responsible for spermatogenesis.[9] They have high gonadotropin levels, while testosterone levels can be low, normal, or even high.[8] There is no treatment option for infertility or to induce spermatogenesis in such cases.[5] Same is the case with our patient who has normal secondary sexual characters and presented with infertility. Although we could not confirm the presence of SRY gene on X chromosome with Fluorescence in situ hybridization (FISH), clinically our patient fits into SRY positive 46, XX testicular DSD.

On the other hand, the SRY negative DSDs commonly have genital anomalies which can lead to diagnosis right after birth or they may present later with gynecomastia, short stature, undescended testes or hypospadias.[7,10] However, cases have been reported of SRY negative 46, XX males with normal sexual development as well.[2,10] The pathogenesis behind this SRY negative testicular DSD might be because of mosaicism of SRY gene in gonads.[11] Another mechanism proposed is SOX9 gene which works with SRY gene for differentiation of gonads into the testes and its over expression can lead to testicular development even in the absence of SRY and microdeletions/duplication in SOX3 have also been linked with SRY negative XX males.[1, 2] A rare syndromic form of SRY negative 46, XX testicular DSD which is associated with palmoplantar hyperkeratosis and squamous cell carcinoma of skin is caused by mutation in R Spondin 1 (RSPO1).[2,12]

The differential diagnosis of this syndrome includes 46, XX ovotesticular DSDs which is characterised by the presence of both ovarian and testicular tissue in the same individual and present with ambiguous genitalia.[13] Our patient did not have any ovarian tissue on ultrasound and

external genitalia were fully developed as male, so this diagnosis was ruled out. Similarly, Klinefelter's syndrome should also be considered in the differential diagnosis which also present with hypergonadotropic hypogonadism like our patient but karyotyping in Klinefelter syndrome is 46, XXY rather than 46, XX, so it was again ruled out.

Interestingly, our patient had a history of brain tumour resection which was reported as Dysembryoplastic neuroepithelial tumour (DNT). It is a well-established benign clinicopathological entity comprising of three components: a glioneural (GN) element, focal cortical dysplasia (FCD), and oligodendrocyte like cells (OLC) intermixed with normal appearing neurons and astrocytes.[14] DNTs are mostly diagnosed in children and young adults at a mean age of 13.8 years, presenting invariably with intractable seizures on initial presentation. DNTs are most frequently observed in the cerebral cortex with a predilection for temporal lobe. The association of DNTs with focal cortical dysplasia points to the mal-development origin of the tumours.[14,15] The benign nature of DNTs stems from their low cellular proliferation potential pointed out in a study conducted on 11 tumours, which concluded a mean MIB1 index (a marker of cellular proliferation) of tumours to be 0.2 (range: 0-0.6).[15] Deformity of the overlying skull, onset of seizures early on in life and focal cortical dysplasia (FCD) usually in the adjacent cortex are the spectrum of clinicopathological features that point to dysembryoplastic origin of the tumour and introduction of the term "dysembryoplastic neuroepithelial tumour".[14] Predominance of DNTs in temporal lobe, their association with FCD and their mixed cellularity suggests that their origin stems from the secondary germinal layer. Moreover, the ultrastructural features of OLC and immunoreactivity of both nestin and MAP2 in OLCs support the idea of origination of DNTs from pluripotent precursor cells.[14]

Brain tumours usually present sporadically but several brain tumours are associated with known genetic syndromes. Approximately 20% of patients with Neurofibromatosis 1 (NF-1) present with some form of CNS tumours, predominantly gliomas. Li–Fraumeni syndrome, Ataxia telangiectasia, Turcot syndrome, Gorlin syndrome, and von Hippel Lindau syndrome are other genetic syndromes which have established associations with CNS tumours.[16] Case reports have also shown the association of dysembryoplastic neuroepithelial tumours with neurofibromatosis type 1 and Arnold-Chiari malformation.[17] But this is the first case of 46, XX testicular DSD with dysembryoplastic neuroepithelial tumour. The syndromic form of SRY negative 46, XX testicular DSD is associated with squamous cell carcinoma of skin and palmoplantar keratosis and DNTs are associated with phacomatosis and Arnold Chiari malformation secondary to the mal-development of foetal central nervous system, so both can be hypothesised for a common origin. This raises the question whether the association of De la Chapelle syndrome with dysembryoplastic neuroepithelial tumour in this case represents a specific association with the underlying cytogenetic abnormality present in this syndrome or whether it is just a coincidence. This necessitates further research to investigate any possible link between the two.

In our case, the androgen replacement therapy with the patient was discussed in detail and the patient was started on injectable testosterone replacement. He was counselled about the fact that fertility is not possible with any treatment. This was quite stressful psychologically for the couple and the patient initially went into denial but later accepted the diagnosis. We recommend that in such cases psychosocial counselling can be very helpful. This relationship/coincidental finding needs further cases to establish any association.

Conclusion

The 46, XX testicular syndrome is quite rare, it can be missed in the differential diagnosis especially when the external and internal genitalia are fully developed as male. This case highlights the fact that in the male presenting for infertility with azoospermia and hypergonadotropic hypogonadism, karyotyping should be performed. Such patients needed long-term androgen replacement and counselling to ameliorate the psychological distress.

Moreover, this is the first case report with 46, XX testicular DSD and Dysembryoplastic neuroepithelial tumour in the same patient.

Consent: Written consent was obtained from the patient for publishing his case.

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Conflict of Interest: None.

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Availability of data and materials: The data related to medical record and laboratory results is available in our computerised data base and the human information maintenance department (HIMS) of Aga Khan Hospital store and maintain the medical record files with a specified medical record (MR) number through which data can be retrieved.

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