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Case Report

Long-term follow-up of a case of Sex Chromosomal Mosaicism with Disorder of Sex Development

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Abstract

Background: Chromosomal mosaicism is characterized by the presence of two or more distinct cell lines in an individual. Mosaicism of sex chromosomes is a major component of Disorders of Sex Development (DSD) and results in a large clinical spectrum of genital ambiguity.

Case Presentation: We report a long term follow-up of a 15-year-old male who was evaluated for ambiguous genitalia with a karyotype of 46, XY (85%) / 46, XX (15%). He presented with an abnormal urethral opening (hypospadias) and a left sided undescended testis since birth. Work-up was done for cytogenetic analysis, hormonal assays, imaging, exploratory laparotomy, and hypospadias repair. For more than 15 years he was reared as a boy, with no further complaints, until he reached puberty. He then developed gynecomastia and monthly painful hematuria. MRI evaluation revealed a left adnexal cystic mass and anteflexed uterus with loculated fluid collection posterior to urinary bladder suggesting hematometra. We discuss the genetics, diagnostics, as well as genetic counselling of this patient.

Conclusion: This case is reported in view of the interesting clinical presentation of this rare mosaicism. A strong emphasis on a multidisciplinary approach and close follow-up is important to ensure both physical and psychological well-being of DSD patients.

Keywords: Disorders of sex development; 46, XY/46, XX; mosaicism
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INTRODUCTION

Chromosomal mosaicism is described as the presence of more than one type of cells within an individual. This condition can be present throughout the entire individual or confined to specific organs, as has been reported in gonads, brain and placenta.[1] Mosaicism has been associated with many genetic disease, pregnancy loss[2], aging and cancer.[3]

Sex chromosome mosaicism results in a large clinical spectrum of disorders of sex development (DSD). The Lawson Wilkins Pediatric Endocrine Society (LWPES) and the European Society for Pediatric Endocrinology (ESPE) in 2006, proposed a new nomenclature and definition of DSD using karyotype as primary root: (1) sex chromosome DSD, (2) 46, XY DSD (disorders of testicular development or disorders in androgen synthesis/action), and (3) 46, XX DSD (disorders of ovarian development or fetal androgen excess).[4]

Individuals with sex chromosomal DSD may develop both ovarian and testicular tissue called ovo-testicular DSD (OT-DSD) which demonstrates distinct tubules in testicular tissue and follicles in ovarian tissue by

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histological analysis.[5] As a consequence, atypical genitalia become an initial manifestation in most cases of OT-DSD. The development of external genitalia may range from apparent female to male genitalia with chordee and hypospadias. The sex chromosomal mosaicisms that have been reported in 33% of OT-DSD cases include : 46, XX/46, XY; 46, XY/47, XXY; 45, X0/46, XY; 46, XX/45, X0; and 46, XX/47, XXY.[6] Successful fertility has been reported in an OT-DSD individual with a male-predominant mosaic karyotype.[7]

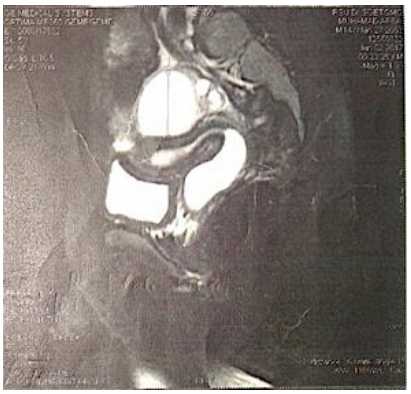

Fig.1 (a)

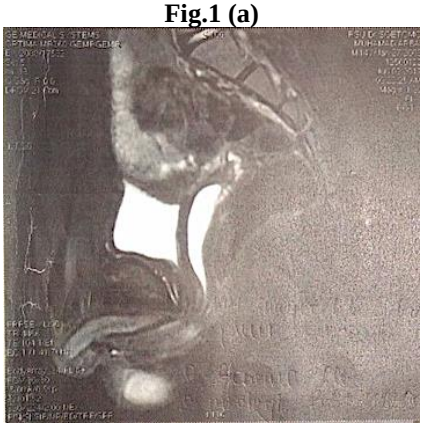

Fig.1 (b)

Fig.1 Sagittal view of pre-operative magnetic resonance imaging (June 2017), revealing (a) right testis and male urethra connecting the urinary bladder to the penis; (b) a vagina and anteflexed uterus with fluid retention.

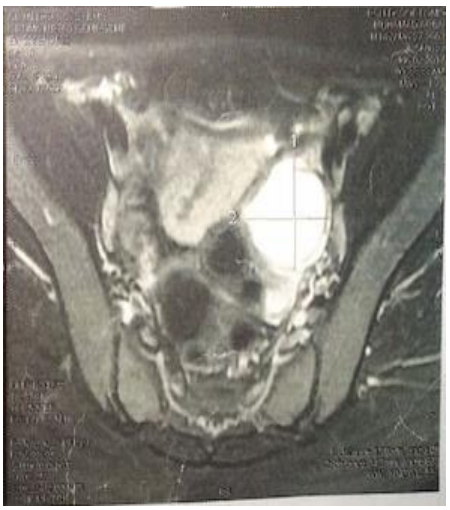

Fig.2

Fig.2 Coronary view of pre-operative magnetic resonance imaging (June 2017), revealing left ovary cyst.

In these cases, a thorough investigation should be performed for a better understanding and comprehensive management of patients. In this report, we describe a case of multidisciplinary management of a patient with sex chromosomal mosaicism and long-term follow-up.

CASE REPORT

An eighteen months old proband, born to a non-consanguineous couple was referred to our center for genetic analysis with the chief complaint of ambiguous genitalia. The patient was subjected to the following scheme of comprehensive examinations: a detailed family history, clinical information, physical examination with photograph taken upon examination with patient consent, hormonal assay, imaging and cytogenetic analysis.

The proband was the 5th born in the family and was reared as a male from birth. There was no history of genetic or congenital disease in the family. On examination of the external genitalia the following features were noticed: stretched penile length (SPL) 3.3 cm, penoscrotal hypospadias with an impalpable left testis while the right sided testis was palpable in the inguinal region with a volume of 1 ml. He had a bifid scrotum with minimal rugosity. The levels of follicle stimulating hormone and luteinizing hormone were lower than normal; 1.32 IU/l (2-7) and 0.15 IU/l (normal:1.5-8), respectively. Subsequently, the 3-day hCG stimulation test showed a significantly increased testosterone secretion (from a basal of <0.1 to 8 nmol/L).

The patient was subjected to cytogenetic analysis (GTG banding) on peripheral heparinized blood which revealed two cell lines: 46, XY (85%) / 46, XX (15%) mosaicism. 100 cells were counted and analyzed. Following this investigation, the hypospadias repair was done in a rural hospital without further follow-up.

For more than 15 years, there were no other complaints until he reached puberty. He started having cyclic hematuria preceded by abdominal cramps. The episodes of hematuria occurred monthly for a duration 3-4 days after he reached age thirteen years. On physical examination, the patient was a slightly built male with well-developed bilateral gynecomastia. The serum level of testosterone was 412.64 ng/dL (241-827), luteinizing hormone: 5.28 mIU/mL (<0.1-6.0), follicular stimulating hormone: 5.49 mIU/mL (1.4-18.1), estradiol: 84.99 pg/mL (0-52), progesterone: 0. 40 ng/mL (0.21-60).

Magnetic resonance imaging can be seen in figure 1, showed vaginal and uterine formation with an endometrial line in an anteflexed position. Fluid retention in the vagina was observed. A left single ovary was seen, which measured 3.7x3.6x3.4 cm cm as shown in figure 2. Urethroscopy revealed a urethra opening located sub-coronally with rough mucosa and a narrow penoscrotal fistula.

DISCUSSION

Chromosomal mosaicism is defined as the presence of intercellular differences in the same individual.[8] Sex

chromosomal mosaicism results in various clinical features of disorders of sexual development (DSD). Genital ambiguity which characterizes sex chromosomal mosaicism is an important point in the management of the patients.

In our study, we report a patient with ambiguous genitalia, diagnosed as sex chromosomal mosaicism, with a long-term follow-up. The patient first came to our clinic for evaluation of ambiguous genitalia when he was eighteen months but there had been no communication with us since then. When the patient finally came for follow up at 15 years old, he had bilateral gynecomastia and urethral bleeding similar to monthly periods. Further investigations revealed Mullerian structures in the patient, implying that the bleeding occurred due to a menstrual cycle.

Any patient with ambiguous genitalia, especially with severe hypospadias and undescended testis should be referred as soon as possible for comprehensive investigation in order to establish the diagnosis, etiology and gender assignment. This includes a thorough clinical examination, family history, hormonal assay, imaging, cytogenetic analysis and molecular investigation. A comprehensive multidisciplinary approach by clinicians is also important for the management of any DSD patients.[9] The expert multidisciplinary team for DSD should include a pediatrician, an obstetrician/gynecologist, a urologist, a geneticist, a surgeon, an endocrinologist, a psychologist and a peer counselor. These disciplines are all important for the comprehensive management of DSD patients. Furthermore, as a part of prevention, follow up on a regular basis is needed to monitor the condition of patients and to address any complications and the risk of malignancy that might occur.

Based on cytogenetic analysis, the presence of two different cell lines 46, XX and 46, XY in this patient could be caused by chimerism (two or more cell lines originated from different zygotes) or mosaicism (different cell lines have emerged from the same zygote).[10] It has been proposed that several possible genetic mechanisms underlie chromosomal mosaicisms. Chromosome non-disjunction, anaphase lagging and endo-replication are several known factors which cause mosaicism.[1] In our case, non-disjunction is unlikely as cause, because the mosaicism in this patient involves two diploid cells with 46 chromosomes, while non-disjunction leads to aneuploidy. The most likely mechanism in this case is therefore chimerism. However, cytogenetic analysis alone may not be able to distinguish chimerism and other mechanism of mosaicism. Molecular investigation is required to allow us to see the differentiation between chimerism and mosaicism.[11]

The gonadal distribution in OT-DSD has been described and may be variable, depending on the karyotypes. OT-DSD with a 46, XX karyotype most commonly have an ovary on one side and an ovotestis on the other side; those with a Y-chromosome have a testis in 61% of cases.[5] In this case, the patient had an ovarian structure on the left side and testis on the other side according to the imaging result. A biopsy of the gonad followed by immunohistochemistry analysis should be performed to confirm the distinction of tubules on the testicular tissue and follicles in the ovarian tissue. As a part of the diagnostic process, the biopsy technique also has an important role. The ratio of testicular to ovarian tissue in OT-DSD may be localized to one side or more evenly distributed in the gonad, therefore a cautious interpretation should be taken into account before reporting the pathology results.[12]

Patients with DSD have a risk for the development of germ cell tumours (GCTs), due to their aberrant germ cell and gonadal development. However, the risk of development of germ cell malignancy in OT-DSD is considered to be low.[13] The diagnosis of germ cell malignancy is characterized by histological evaluation of gonadal tissue followed by positive staining for expression of OCT3/4 and TSPY. The OCT3/4 protein is expressed at the basal lamina and under tight junctions between the Sertoli cells of the gonad which has turned into a malignant GTC. Therefore, to rule-out the probability of GCTs in our patient, the biopsy and immunohistochemistry staining should be carried out. It is important in follow-up to elucidate GTC precursor lesions which is Carcinoma in Situ (CIS), consisting of germ cells blocked in their physiological process of maturation. However, no specific markers are available yet to distinguish germ cells that are delayed in their maturation from those undergoing malignant transformation. Subsequently, monitoring of testicular imaging followed by β-hCG and α-fetoprotein serum levels would be needed for assessing the risk of development of GTCs.[14]

In OT-DSD, the gonad may contain ovarian and testicular tissue. The developing ovary may lead to a functional ovarian tissue which causes menstruation in 50% of cases of OT-DSD.[5] The production of ovarian steroids can also suppress expression of gonadotropins in testicular tissue via a negative feedback effect, resulting in tubular atrophy, poor germ cell development, Leydig cell hyperplasia, and sclerosis that finally causes degeneration of the testicular tissue.[15] As the testosterone production may decline to inadequate levels because of the testicular regression, the consideration of substitutive hormonal treatment should be initiated.[14]

An infant born with ambiguous external genitalia presents a major challenge, not only for establishing the diagnosis but also the complexities surrounding any decision about gender assignment. A comprehensive multidisciplinary team is essential in order to provide the best of care for patient with DSD followed by psychological support for the patient, and also family members. In this patient, gender assignment as male was made based on evaluation of gender identity and gender role by the multidisciplinary team in our center, taking into account the patient's wish. Since the patient has not reached the legal age to make a medical decision, parental consent and patient assent were obtained as part of this process, and parental support for the transfer of information and the strategies greatly helped the clinicians to deliver the best possible treatment for the patient. In this context, we recommended gonadal detection, biopsy, and selected removal of ovarian tissue followed by genitoplasty to confirm the male gender assigned. Serial measurement of estradiol should also be

carried out to confirm absence of residuary ovarian tissue. Due to the potential risk of the testicular regression, hormonal evaluation and hormone replacement may be given to maintain secondary sexual characteristics. Longitudinal follow-up is required to avoid adverse effects that may occur due to gonadal insufficiency and inherent risk of malignancy.

CONCLUSION

Several findings in this patient shed more light on the complexities of the OT-DSD condition. This case highlights the importance of a multidisciplinary team, genetic counselling and long-term follow up for a comprehensive evaluation and treatment of DSD.

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REFERENCES

1. Taylor TH, Gitlin SA, Patrick JL, Crain JL, Wilson JM, Griffin DK. The origin, mechanisms, incidence and clinical consequences of chromosomal mosaicism in humans. Hum Reprod Update 2014;20:571-81.
2. Hassold T, Hunt P. To err (meiotically) is human: the genesis of human aneuploidy. Nat Rev Genet 2001;2:280-91.
3. Vijg J. Somatic mutations, genome mosaicism, cancer and aging. Curr Opin Genet Dev 2014;26:141-9.
4. Hughes IA, Houk C, Ahmed SF, Lee PA. Consensus statement on management of intersex disorders. Arch Dis Child 2006;91:554-63.
5. van Niekerk WA, Retief AE. The gonads of human true hermaphrodites. Human Genetics 1981;58:117-122.
6. Nistal M, Paniagua R, Gonzalez-Peramato P, Reyes-Mugica M. Perspectives in Pediatric Pathology, Chapter 7. Ovotesticular DSD (True Hermaphroditism). Pediatric and developmental pathology : the official journal of the Society for Pediatric Pathology and the Paediatric Pathology Society 2015;18:345-52.
7. Schoenhaus SA, Lentz SE, Saber P, Munro MG, Kivnick S. Pregnancy in a hermaphrodite with a male-predominant mosaic karyotype. Fertility and sterility 2008;90:2016 e7-10.
8. Iourov IY, Vorsanova SG, Yurov YB. Chromosomal mosaicism goes global. Mol Cytogenet 2008;1:26.
9. Hiort O, Birnbaum W, Marshall L, et al. Management of disorders of sex development. Nature reviews Endocrinology 2014;10:520-9.
10. Malan V, Vekemans M, Turleau C. Chimera and other fertilization errors. Clin Genet 2006;70:363-73.
11. Conlin LK, Thiel BD, Bonnemann CG, et al. Mechanisms of mosaicism, chimerism and uniparental disomy identified by single nucleotide polymorphism array analysis. Hum Mol Genet 2010;19:1263-75.
12. Moriya K, Morita K, Mitsui T, et al. Impact of laparoscopy for diagnosis and treatment in patients with disorders of sex development. J Pediatr Urol 2014;10:955-61.
13. Looijenga LH, Hersmus R, Oosterhuis JW, Cools M, Drop SL, Wolffenbuttel KP. Tumor risk in disorders of sex development (DSD). Best Pract Res Clin Endocrinol Metab 2007;21:480-95.
14. Scarpa MG, Grazia MD, Tornese G. 46,XY ovotesticular disorders of sex development: A therapeutic challenge. Pediatr Rep 2017;9:7085.
15. Mao Y, Chen S, Wang R, Wang X, Qin D, Tang Y. Evaluation and treatment for ovotesticular disorder of sex development (OT-DSD) - experience based on a Chinese series. BMC Urol 2017;17:21.