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46,XX/46,XY Chimera with Ovotesticular Disorder of Sex Development (OT-DSD): A Rare Entity

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Abstract

Ovotesticular disorder of sex development (OT-DSD) is a condition in which, both testicular tissue and ovarian tissue are co-existent in the same gonad (ovotestis) or independently in separate gonads characterizing the anatomical form of lateral ovotestis. Here, in this study, we report a case of lateral ovotestis associated with a chimera, Chi 46,XX/46,XY. He presented for fertility assessment and karyotyping because of DSD characterized by gynecomastia associated with hypospadias; Karyotyping of peripheral blood revealed a 46,XX/46,XY chimeric condition confirmed by SNP array analysis. After surgical exploration, an hemi-uterus with its tube and gonad was found and remove. Histology revealed ovarian tissue with follicules at different stage while semen analysis revealed a severe oligoastheno teratozoospermia. A gonad was palpable on the right hemiscrotum and ultrasound showed a testis structure. The patient clamed conservation of its testicle and requested bilateral mastectomy. A multidisciplinary approach was warranted to establish this rare entity's diagnosis and its management. In the case of gonad preservation, the risk of gonadoblastom is to be discussed and follow up recommended.

Keywords

Ovotestis-Disorder of Sex Development-DSD-Chimera, Hypospadias

1. Introduction

Ovotesticular disorder of sex development (ovotesticular DSD) is a rare condition characterized by the presence of both ovarian and testicular tissue within the same

gonad (ovotestis) or independently in separate gonads (lateral ovotestis) [1].

This can result in a range of phenotypic manifestations, including ambiguous genitalia, micropenis and cryptorchidism [2]. The prevalence of ovo testis is estimated at less than 1:20,000 births [3] with an overall estimation of less than 5% of all DSD [4]. According to Wiersma *et al.* [5], the most widespread associated karyotype is type 46,XX with a prevalence of 69%, with more rarely a chimeric form 46,XX/46,XY representing 1% of all ovotestis [6].

Chimerism is defined by the presence of two genetically distinct cell lines within the same individual [7]. Only a few cases of chimerism has been described in the literature and the most recent and exhaustive review at this day, was published in 2020 and collected 52 cases from NCBI data base since 1963 [7].

The interplay between ovotesticular DSD and chimerism is complex and not fully understood [8].

The management is multidisciplinary and here by this study, we present a case of this association concerning a patient who benefit from a standard and molecular Karyotype and who underwent a surgery to remove intra abdominal gonad because of risk of malignant degenerescence. Thus, we propose a mini review concerning this particular and rare entity.

2. Case Presentation

SK, aged 31, was referred to our Cytogenetics and Reproductive Biology Unit for fertility assessment and karyotype. He was being monitored for hypospadias and desire for parenthood. He had a male first name and was a shepherd. He measured 184 cm and weighed 72 kg.

Puberty would have started around the age of 13 years and was marked by the appearance of gynecomastia confirmed by physical examination. Examination of the external genitalia reveals the presence of a small penis with a urethral orifice at the perineal junction, associated with posterior penoscrotal hypospadias. Only one testicle is palpated in the right scrotum.

Ultrasound identified a testicle with a normal echo structure in the right scrotum. However, an oblong mass with an inhomogeneous echo structure measuring 30 mm in diameter was identified in the left pelvic area.

3. Materials and Methods

3.1. Semen Analysis

Semen was collected by masturbation and after one hour of liquefaction, parameters were established according to WHO semen guide for semen analysis version 2010. Morphology was assessed by using Kruger criteria [9].

3.2. Standard Karyotyping

Chromosomes were obtained after culturing lymphocytes from peripheral blood by adding appropriated media culture and phytohemagglutinin according standard techniques.

R banding was performed and metaphases were selected and analyzed using a LEICA DM2500 microscope equipped with a camera and Cytovision CW4000 image software analysis.

3.3. SNP Array

A genome-wide analysis was performed using Human CytoSNP-12v2.1 Analysis BeadChip (Illumina) according to the adequate protocol with an input of genomic DNA. Scan data were visualized using iScan system (Illumina). Analysis was performed with Illumina Genome Studio V2001.1 and Illumina Karyostudio1.4.3.0. according to UCSC Genome browser. Results were confirmed by the collaboration with an external lab (Eurofins Biomnis).

3.4. Gonadal Histology

The operative pieces were obtained after resection of an hemi-uterus associated with a tube and gonad, Operative pieces were fixed on formalin, dehydrated and paraffin-embedded. Slides were prepared after obtaining Samples of 4 µm thickness, and after deparaffinization and routine staining (HE) Histopathologic analysis was performed.

4. Results

4.1. Semen Analysis

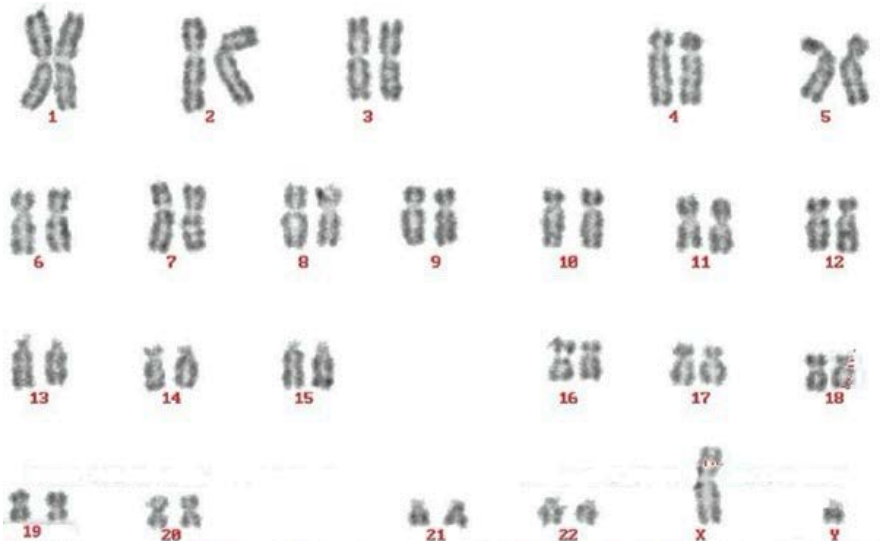
Sperm analysis revealed severe oligoasthenoteratozoospermia. Semen parameters were the following: 1.5 mL of semen, a concentration of 1.8 million spermatozoa/mL, 15% mobility for mobile progressive spermatozoa, 20% of vitality, and 2% of typical forms (**Figure 2(B)**).

4.2. Standard Karyotyping

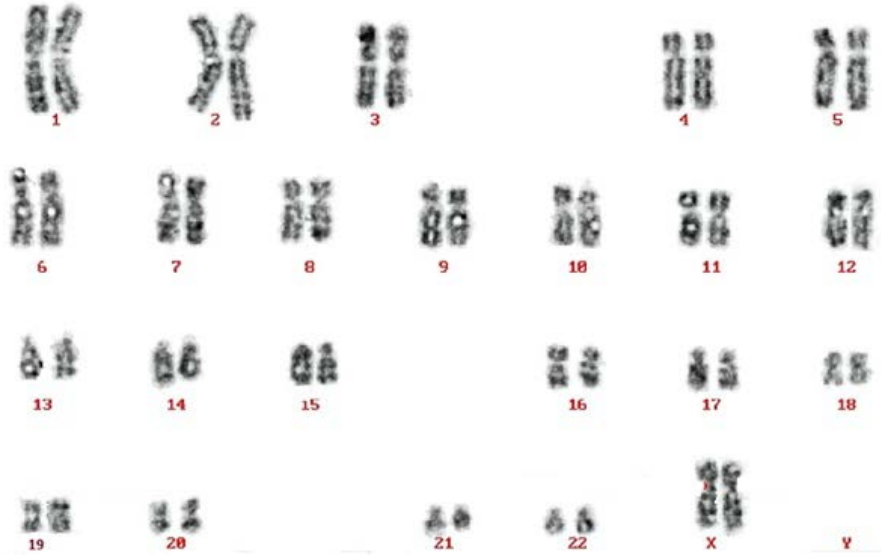
R-band karyotyping, performed using the above-mentioned technique, revealed a chimeric formula Chi 46,XX/46,XY. The first classification of 30 metaphases allowed the detection of a 46,XX clone with 26 cells (**Figure 1(A)**) and a second clone containing 4 cells of type 46,XY (**Figure 1(B)**). We extended then the classification to 95 cells, confirming a percentage of 90 % for 46,XX clone and 10% for 46,XY cell clone.

4.3. SNP Array

A second blood sample collected in EDTA was analyzed by DNA chip (SNP-array), in a reference laboratory (Eurofins Biomnis). This examination formally excluded the diagnosis of mosaicism and confirmed the diagnosis of a chimera. Thanks to the molecular karyotype, the presence of 2 distinct cell populations was identified, including a majority population, 46,XX estimated at around 90% and a minority population 46,XY estimated at around 10%. The formula, arr(1-22)x2,(X)x2[0.90],(X,Y)x1[0.90], was established according to the nomenclature of the ISCN 2016 guide.



(A)



(B)

Figure 1. Karyotype results with two sets; (A) 46,XY formula and (B) 46,XX formula.

4.4. Surgical Exploration and Histology of the Gonads

After exploration of the pelvis, a hemi-uterus was identified as well as a tube and a whitish structure with an ovarian appearance. This ovarian-looking gonad was lateralized to the left in the pelvis.

At the patient's request, a mastectomy and removal of the female-type internal organs were performed. The patient received hormone therapy with the administration of androgens.

The anatomopathological examination revealed macroscopically the presence of a tube with a hemi-uterus and an ovary, confirmed microscopically by the presence of a parenchyma containing ovarian follicles at varying degrees of maturation (**Figure 2(A)**).

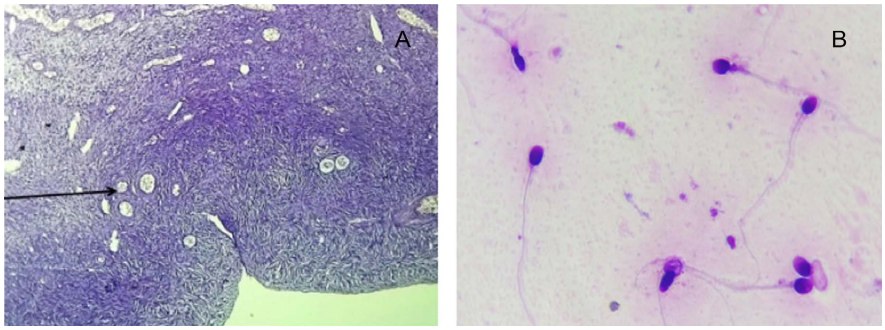


Figure 2. (A) Ovarian tissue with oocytes at different stages of maturation; (B) Spermatozoa morphology after semen analysis.

5. Discussion

5.1. OT DSD Prevalence and Karyotype Pattern

Ovotesticular disorder of sex development (OT-DSD) replaced the terminology of true hermaphrodite in 2006, during the consensus of Chicago [10]. This entity constitutes 3% to 10% of the total DSD and presents significant diagnostic and therapeutic challenges [11]. The cytogenetic aspects of OT-DSD vary depending on geographic location. In South Africa, the most common karyotype in OT-DSD is 46,XX (88%), followed by 46,XY (8%), 46,XY/45,X (3%), and 46,XX/46,XY (1%) [6]. On the other hand, in Japan, according to Matsui [12], the 46,XY karyotype was the most common form. In Europe, the most common karyotype would be 46,XX (53%) followed by cases of mosaicism and chimerism (40%) [13].

The genetic basis of specific types of disorders of sex development (DSD) remains partly unexplained [2] Identification of the presence of chimerism can be relevant in the context of elucidation of the genetic mechanism underlying ovotesticular-DSD (OT-DSD) knowing that OT DSD is defined by both presence of ovarian et testicular tissue. Indeed, at cytogenetic level, the presence of 2 cells lines as 46,XX and 46,XY able to induce respectively female and male differentiation of gonads could explain the presence of the two tissues. Nevertheless, about 60% of patients with OT DSD have 46,XX chromosomal formula [14]. This suggests that this phenotype could be explained by other variations at molecular level, as suggested by (Bashamboo *et al.*) [15].

5.2. Chimerism

A chimera is defined by the fusion product of two different zygotes in a single embryo, and its incidence is still unknown [16]. It is a rare condition. In 2020, Madan *et al.* [7] reviewed 52 cases collected since 1963. Since then, to our knowledge, six more cases have been reported in the NCBI PubMed base (**Table 1**). The prevalence of natural human chimeras is hypothesized to be as high as 10%, and as far as it is probably completely unknown for humanity [7]. Suspicion of Chimera comes to medical attention when 46,XX/46,XY formula is found after karyotyping, but in some cases, normal karyotype was reported. Even with some clinical signs like Blashko line [17], the suspicion diagnosis is not evident, and the real

percentage is probably underestimated. Chimerism may concern cases in phenotypically normal women [18] or normal men [19]. Some cases of normal pregnancy have been reported [20]. Thus, Bottega *et al.* [21] suggest that this phenomenon might be probably underdiagnosed, as all chimeric individuals would not be detectable by standard cytogenetic technology.

Table 1. Cases repertoried in the NCBI PubMed database since 2020.

Author	Sexual Phenotype	Karyotype	Type of chimera mechanisms
Hercent A *et al.*, 2020 [28]	P1 phenotypically normal infertile man	46,XX/46,XY	Not explored
	P2 phenotypically normal infertile man presenting with idiopathic non-obstructive azoospermia	46,XX/46,XY	Not explored
	P3 children boy with a gonad corresponding to an ovary/disorder of sex development	46,XX/46,XY	Not explored
Charalsawad C *et al.*, 2022 [29]	DSD (Ambiguous genitalia)	47,XY, +21/46,XX	Tetragametic chimera fertilization with two spermatozoa, one with an ovum and the other with the second polar body.
He Y *et al.*, 2024 [30]	Adult with normal male phenotype and idiopathic infertility with oligoasthenoteratozoospermia	46,XX/46,XY	Parthenogenetic chimera
Chen L, 2024 [31]	Prenatal diagnosis of a Male with normal phenotype at birth	46,XY/46,XY	Tetragametic chimera Fertilization of two ova by two spermatozoa, followed by the fusion of the two early embryos

5.3. New Trends in Diagnosis Strategy of Chimerism

Historically and classically, chimerism diagnosis is confirmed after short tandem repeat (STR) analysis using PCR and quantification of specific genetic differences (*i.e.*, polymorphic markers) and classical cytogenetics (Karyotyping) [22]. Later, with the development of molecular cytogenetics, detection of chimerism has become feasible with the application of targeted tests as well as genome-wide single nucleotide polymorphism (SNP) analyses [23]. In the case of our patient, the analysis of the B-allele frequency of autosomes and the X chromosome revealed the presence of two different genomes, excluding mosaicism. Indeed, in the case of chimerism, SNP array results show a diffusely altered pattern of B allele frequencies (BAF) along all the autosomes that is consistent with the coexistence of two different genotypes with an altered ratio between the two haplotypes. Bottega *et al.* [21] suggest that the routine use of genotyping SNP array analysis would be helpful for the identification of "hidden" chimerism in patients presenting a few clinical clues such as Blashko lines, et cetera. According to Sheets *et al.* [24] SNP-based microarrays, also have limitations, as the lower limits of detection of chimeras using this platform are currently unknown. Conlin *et al.* [23] were able to

detect a chimeric XX/XY individual using SNP-array technology with a sample estimated to have between 20% to 45% chimeric cells present. The author predicts SNP-based assays to be capable of detecting samples with as low as 5% chimerism.

On the other hand, STR would also have limitations as a test when performed to study the mechanism of the chimera by identifying the origin of the alleles inherited from the parents. Indeed, STR has been in the past responsible for false negative parental tests, precisely when the excluded parent was a chimera [24] [25]. As suggested by Sheets *et al.* [24], a better understanding of the detection limits of STR, SNP-microarrays and other DNA tests utilized in diagnosing and detecting chimerism is needed. Indeed, single-cell sequencing could be a clue, allowing a better understanding of chimera and giving an idea about its real prevalence among humans.

5.4. Mechanisms of Chimera

In the case of our patient, the proband's parents were not available to discriminate the parental allelic contribution and assess the mechanism of the chimera. Three main mechanisms are described It concerns tetragametic chimera, andro or gynogentic chimera and pathogenetic chimera [7]. Tetragametic chimeras are known as the most common subtype and are formed by fusion of two fertilized ova or by fusion of a fertilized 2nd polar body with a fertilized ovum Androgenetic chimera and gynogenetic chimera. Androgenetic chimeras are formed by duplication of the male pronucleus, fertilization of the ovum by one male pronucleus, and diploidization of the other. Gynogenetic chimera are formed by parthenogenetic division of the female pronucleus, fertilization of one daughter cell by a sperm, and diploidization of the other. Parthenogenetic chimera are formed by parthenogenetic division of the ovum duplication of the female pronucleus, followed by fertilization of the two female pronuclei by two spermatozoa [23].

5.5. Malignant Degenerescence

In the case of association with OT DSD, patients are at a high risk of malignancy, including gonadoblastoma, dysgerminoma/seminoma, and yolk sac tumors. Due to the risk of malignant degeneration, monitoring is recommended with early recourse to surgery if necessary to avoid malignant degenerescence. Nevertheless, tumoral risk is reported to be lower compared to other cases of DSD [26] with an estimated prevalence of 2.5 - 4 [27].

6. Conclusion

The diagnosis of ovotestis and chimerism is a rare entity of DSD. The analysis of our case highlights the importance of analyzing a large number of cells in classical cytogenetics to avoid missing the diagnosis. Chimeras can be even more difficult to detect, especially when the sexual formula turns out to be normal. In our case, the performance of SNP array analysis was of great help, allowing an accurate diagnosis and exclusion of abnormalities due to duplications or deletions at the

resolution scale of the technique. Regarding the literature, it seems that a better understanding of the limits of utilized tests like STR and SNP microarray, to diagnostic chimera is needed. Due to the risk of malignant degeneration, monitoring is recommended with early recourse to surgery if necessary to avoid gonadoblastoma.

Ethical Considerations

Our patient received explicit information regarding the scientific disclosure of the results and images. Thus, written consent by the patient for publication of this case report and any accompanying images was obtained.

Limitations

In the absence of the parents, the mechanism of the chimera could not be determined.

Conflicts of Interest

We, the authors, declare that we have no conflict of interest.

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