

## Case Report

# A Case Series of Five Sri Lankan Patients with Ovotesticular Disorder of Sex Development

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**Abstract.** Ovotesticular disorder of sex development (OT-DSD) is a rare disorder of sexual differentiation in which the gonads of an individual are characterized by the presence of both mature ovarian and testicular tissues. The objective of this paper is to report the clinical, cytogenetic and histopathological findings in Sri Lankan patients diagnosed with OT-DSD who were referred to the Human Genetics Unit for cytogenetic evaluation during 2005 to 2011. Five patients had histopathologically confirmed OT-DSD. Their ages at presentation ranged from 2 mo to 47 yr. Clinical symptoms varied from ambiguous genitalia and inguinal hernias at birth to a lower abdominal mass presenting in adulthood. All 5 were reared as phenotypic males. An ovotestis was detected in all cases except one, and the predominant karyotype was 46,XY. The findings in this series of predominantly 46,XY karyotype are in contrast to previously published reports that have reported 46,XX as being the predominant karyotype. It is therefore recommended that individuals with ambiguous genitalia who have the 46,XY karyotype should be thoroughly investigated by ultrasonographic or laparoscopic assessment to determine the exact nature of their internal genital organs. OT-DSD should also be considered in the differential diagnosis of patients with cryptorchidism and inguinal hernia.

**Key words:** ovotestis, true hermaphroditism, disorder of sex development, ambiguous genitalia

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## Introduction

Ovotesticular disorder of sex development (OT-DSD) is a rare disorder of sexual differentiation characterized by the presence of testicular tissue with distinct seminiferous tubules and ovarian tissue with mature ovarian follicles in the same gonad (ovotestis) or separately in a single individual (1, 2). OT-DSD

replaced the term “true hermaphrodite” in 2006 (2). It constitutes between 3 and 10% of the total DSD and presents significant diagnostic and management challenges (3, 4). Typically, both Mullerian and Wolffian duct derivatives are seen, and most affected individuals commonly present with ambiguous external genitalia as neonates or infants. However, the phenotype of the external genitalia may range from normal male to normal female depending on the degree of testicular tissue present. The ovotestis is usually the most common gonad in individuals with OT-DSD, and such gonads are known to be at an increased risk of developing germ cell tumors (5).

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More than five hundred cases of OT-DSD including familial cases have been reported in medical literature (3, 6, 7). Epidemiologically, the geographical distribution of OT-DSD shows a higher prevalence in the African continent, especially among South African blacks, with the number of published cases being 17 per 100 million people, followed by Europe at 15.3. Asia is under-represented at 1.2 cases per 100 million (8). Age and mode of presentation is often variable and usually comprises hypospadias, unilateral or bilateral cryptorchidism, inguinal hernia, urogenital sinus, gynecomastia at pubertal age or lower abdominal mass in adulthood (4). Internally, the presence of an ovotestis is the most common finding followed by ovaries (4, 9).

The chromosomal findings in OT-DSD were first reported in 1959 by Hungerford, who demonstrated a 46,XX chromosomal complement in peripheral blood lymphocytes of an individual with this disorder (10). OT-DSD is a genetically heterogeneous condition with the predominant karyotype being 46,XX, while 46,XX/46,XY chimerism, 46,XY karyotype and X-Y translocation are less frequent (4). The objective of this paper is to describe the diverse clinical, cytogenetic and histopathological features of five patients diagnosed with OT-DSD in Sri Lanka.

### Case Report

This is a report of the clinical, cytogenetic and histopathological data of patients with OT-DSD who were referred to the Human Genetics Unit for cytogenetic evaluation between 2005 and 2011. This facility serves as the main referral center for cytogenetic testing in Sri Lanka, and the majority of children with DSD in the country undergo karyotype testing at this center. All patients had given written informed consent for cytogenetic testing. In the case of children, this was given by the parents. Detailed clinical history and physical features were obtained from the patients' medical records. The diagnosis of OT-DSD had been confirmed by histopathological

examination of the gonads, which were biopsied either laparoscopically or at exploratory laparotomy. Five milliliters of peripheral blood was obtained from each patient, and chromosomal analysis was performed on routinely cultured lymphocytes after GTG-banding. Karyotyping was done according to guidelines of the International System for Human Cytogenetic Nomenclature (ISCN, 2005). At least 30 well-spread and well-banded metaphases were examined in each patient by an experienced cytogeneticist.

There were five patients with histopathologically confirmed OT-DSD. The age, sex of rearing, mode of presentation, status of the external and internal genitalia and karyotypes of the patients are summarized in Table 1. Their ages ranged from 2 mo to 47 yr, and all were reared as males. In four of the patients (cases 1, 3, 4 and 5), ambiguous genitalia were noticed at birth. Two patients (cases 1 and 3) had perineal hypospadias with bilateral cryptorchidism, while the other two patients (cases 4 and 5), who were siblings, both had male external genitalia with a short, blind-ending vagina and bilateral inguinal lumps. Case 2 was reared as a male but started feminizing and developed female secondary sexual characteristics at puberty with gradual atrophy of both testes. Case 1 underwent surgical correction for perineal hypospadias during early childhood but remained undiagnosed until an exploratory laparotomy performed for an intra-abdominal lump led to the diagnosis of OT-DSD at the age of 47 yr. In addition to the lower abdominal mass, this patient was observed to have gynecomastia. Inguinal lumps in association with cryptorchidism were observed in 3 cases. Two patients had bilateral ovotestis: one had an ovotestis on one side and an ovary on the other side, the other had an ovotestis on one side and a testis on the other side; the remaining patient had an ovary and testis separately on either side. Four patients (cases 1, 2, 4 and 5) had a 46,XY chromosome complement, while 46,XX/46,XY chimerism was

**Table 1** Profiles of the five patients with ovotesticular disorder of sex development

Case	Age	Sex of rearing	Indication for investigation	External genitalia	Internal genitalia/gonads	Karyotype
1	47 yr	Male	Ambiguous genitalia at birth/abdominal mass in adulthood	Perineal hypospadias, bilateral cryptorchidism	Uterus with tubes, left ovotestis and right testis	46,XY
2	23 yr	Male	Female secondary sexual characteristics at puberty with gynecomastia	Male external genitalia with bilateral atrophic testes	Uterus with tubes and bilateral streaky ovaries and atrophic testes	46,XY
3	2 mo	Male	Ambiguous genitalia/inguinal lump	Perineal hypospadias, bilateral cryptorchidism	Uterus with tubes, left ovary and right ovotestis	46,XX/ 46,XY
4	9 mo	Male	Ambiguous genitalia/bilateral inguinal lumps	Male external genitalia with blind-ending vagina	Uterus with tubes and bilateral ovotestis	46,XY
5	5 yr	Male	Ambiguous genitalia/bilateral inguinal lumps	Male external genitalia with blind-ending vagina	Uterus with tubes and bilateral ovotestis	46,XY

observed in the remaining patient (case 3). There were no cases of 46,XX karyotype.

### Discussion

OT-DSD is a rare disorder of sexual differentiation that is phenotypically and genetically heterogeneous with wide-ranging manifestations. The presence of well-differentiated ovarian and testicular tissue in the same individual, whether as a single tissue-type gonad or an ovotestis, is the hallmark of this condition (9). Most patients with OT-DSD have ambiguous genitalia and are often diagnosed within the first few months to years of life (1, 4, 9). In addition to ambiguous genitalia, patients may present with inguinal hernias, gynecomastia during adolescence or lower abdominal mass in adulthood (4, 11). These observations are reflected in the patients reported in this paper. Four out of 5 patients in this series had ambiguous genitalia diagnosed in the first few months to

years of life, and all were reared as phenotypic males. Inguinal hernias and gynecomastia were also present in some patients. A small number of OT-DSD cases are incidentally picked up during laparotomy for unrelated causes. One of the patients in this series had a similar presentation; he presented with a lower abdominal mass in the fourth decade that was later discovered to be an 18-wk-size uterus at laparotomy. A similar case of OT-DSD in a 42 yr old was reported in North India (4). In OT-DSD, the degree of virilization of the external genitalia depends on the capacity of the testicular tissue to secrete testosterone. Previous studies indicate that although approximately 70% of OT-DSD patients are raised as males, less than 10% have normal male external genitalia (1). It is generally believed that the Leydig cell function of the dysgenetic testis is inadequate for normal virilization (4), and this is exemplified in this series by case 2, who had bilateral atrophic testes and started feminizing at puberty. Previous

reports have also indicated that testicular tissue in OT-DSD patients becomes dysgenetic and that germ cells begin to disappear with increasing age (12).

The patients in this study had internal genital organs ranging from streaky ovaries and a uterus to atrophic testes, but the common presenting gonad was the ovotestis. It is known that gonadal tissue may be located at any level along the route of embryonic testicular descent and is frequently associated with an inguinal hernia. A sub-classification of OT-DSD based on the type and location of the gonads has been described (13). According to this classification, OT-DSD is considered to be lateral if a testis is present on one side and an ovary is present on the other side (case 2), unilateral if an ovotestis is present on one side and a testis or ovary is present on the other side (cases 1 and 3) and bilateral if an ovotestis is present on both sides (cases 4 and 5). Damiani *et al.* (9) reported that the ovotestis was the most frequent gonad, accounting for 59% in their series of 16 patients with OT-DSD, and Krob *et al.* (3) also reported that an ovotestis was found in 44.4% of 568 gonads examined. The same observation is reflected in this series, in which 4 out of 5 cases (1, 3, 4 and 5) had an ovotestis and 2 of the patients, who were siblings, had bilateral OT-DSD. With regard to the frequency of gonadal distribution, it is reported that the most common form is ovotestis plus ovary followed by bilateral ovotestis and ovary on one side and testis on the other side, representing 34%, 29% and 25% of cases, respectively (8). Previous studies have reported that the risk of germ cell tumors, especially dysgerminomas, in patients with OT-DSD ranges from 4% among those with the 46,XX karyotype to up to 10% in those with 46,XY and 46,XX/XY chimerism (4, 5). No gonadal tumors were identified in any of the patients in this study.

Analysis of the chromosomal distribution of OT-DSD shows that about 50–65% cases have a 46,XX chromosomal constitution followed by

46,XX/46,XY chimerism, while less than 10% have a 46,XY karyotype (1, 8, 9). The 46,XY karyotype is believed to be extremely rare and equally distributed throughout Asia, Europe and North America (3). In contrast to published reports (3, 4, 8, 9, 14), the predominant karyotype was 46,XY in 80% of the patients in this series. There is no apparent reason for 46,XY being the most common karyotype in this study other than the small number of patients studied, with possible over-representation of the 46,XY karyotype in this study sample, or it could be reflective of the pattern seen in the Sri Lankan population. Karyotypes such as 46,XX/46,XY, which was seen in only one patient, are thought to result from chimerism, possibly from double fertilization (involving two spermatocytes—one X and one Y) of either a binucleate ovum or of an ovum and its polar body (15).

In some of the patients, proper investigation and accurate diagnosis had been delayed for many decades in spite of ambiguous genitalia being detected early in life, which led to clinical and psychological problems in their adult life. It is therefore recommended that in addition to cytogenetic evaluation, phenotypic males with ambiguous genitalia should be thoroughly investigated by means of either abdominal ultrasound scan and/or exploratory laparoscopy/laparotomy with histopathological examination to properly assess the exact nature of their internal genital system. Although considered a rare presentation, the cases reported in this series suggest that abnormal inguinoscrotal or abdominal masses may occur in OT-DSD and should be considered in the differential diagnosis of patients, especially in those with cryptorchidism and inguinal hernia having the 46,XY karyotype.

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