Monozygotic Twins with Discordant Sexual Phenotypes due to Different Ratios of Mosaicism of 47,X,idic(Y),idic(Y)/46,X, idic(Y)/45,X

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Abstract. We report monozygotic twins of different sexual phenotypes. One of the twins had complete female external genitalia except for a mild clitoromegaly. She had bilateral gonads consisting of the wavy stroma and scant dysgenetic seminiferous tubules. No androgen secretion was induced by gonadotrophin stimulation. The other twin had hypospadiac male genitalia. His gonads were located intrascrotally and he had good androgenic response to a stimulation test. Conventional and fluorescence in situ hybridization chromosome analysis disclosed that both twins had a 47,X,idic(Y),idic(Y)/46,X and 47,X,+mar×2,ish idic(Y)(q11.2)(DYZ3++×2)/46,X,+mar,ish idic(Y)(q11.2)(DYZ3++)/45,X. These twins were clinically monochorionic and allelotypic analysis in these twins and their parents with microsatellite markers showed the affirmative probability of 0.999999994 for monozygosity. The ratio of mosaicism, gonadal histology, and testosterone productivity were reasonably correlated to the genital virilization in these monozygotic twins, showing discordant sexual phenotypes.

Key words: Mixed gonadal dysgenesis variant, Mosaic karyotype, Discordant sexual phenotypes, Monozygotic twins


INDIVIDUALS with sex chromosome mosaicism such as 45,X/46,XY manifest a highly diverse phenotype, ranging from phenotypic females to individuals with ambiguous external genitalia to phenotypic males [1, 2]. The degree of masculinization of external genitalia is affected by the amount of systemic circulating androgen secreted mainly from the fetal testis [3]. Monochorionic twins often show discordance for birth weight, genetic disease and congenital anomalies, but rarely for genital phenotypes [4, 5]. We recently encountered monochorionic twins with 47,X,idic(Y),idic(Y)/46,X,idic(Y)/45,X manifesting discordant sexual phenotypes. One twin had complete female genitalia, while the other had hypospadiac male genitalia.

Patients

Twin 1

The first twin had a birth weight of 1,444 g and a blood hemoglobin concentration of 15.8 g/dl. The child had coarctation of the aorta, right inguinal hernia and female external genitalia with minimal clitoromegaly (Fig. 1a). Conventional chromosome analyses of the peripheral lymphocytes revealed sex chromosome mosaicism of 45,X/46,X,idic(Y)/47,X,idic

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Fig. 1. Sexual organs of Twin 1. Clitoral enlargement is less than 1 cm in diameter (a), gonadal histology showing wavy fibrous stroma surrounds the scanty dysgenetic seminiferous tubules (b) (Original magnification: ×200), and laparoscopic view indicating the presence of the uterus, bilateral oviducts and right the gonad without the tunica albuginea (c). U: uterus; asterisk (*): right gonad.

(Y), idic(Y) and their proportions of the respective cell lines in the buccal cells were 58.4/38.0/3.6%. Fluorescence in situ hybridization (FISH) analysis revealed a structural Y chromosome abnormality of 45,X/46,X,+mar.ish idic(Y)(q11.2)(DYZ3+++/47, X,+mar ×2.ish idic(Y)(q11.2)(DYZ3+++/2), respectively. Serum testosterone and estradiol were not increased to hCG/hMG administration at all. LH-RH test revealed an excess gonadotropin response (Table 1). After surgical repair of the aortic coarctation, genitescopy and laparoscopy with gonadal biopsy were performed at one year of age. The bilateral internal sexual organs were female ones. Bilateral streak gonads consisted of trace testicular structures (Fig. 1b). At two years of age, she underwent bilateral laparoscopic gonadectomy concomitant with the staple clipping of bilateral oviducts (Fig. 1c) and right inguinal herniorrhaphy.

Twin 2

The second twin had a birth weight of 1,846 g and a blood hemoglobin concentration of 17.1 g/dl. The baby did not have coarctation of the aorta as did Twin 1. But, he had severe hypospadias and a bifid scrotum. Gonads were palpated bilaterally in the scrotum (Fig. 2a). Conventional and FISH chromosome analyses of the peripheral lymphocytes revealed that he had same chromosome abnormality as Twin 1: 47,X,idic(Y),idic(Y)/46,X,idic(Y)/45,X with proportions of 62.4/31.4/6.0% and 47,X,+mar ×2. ish,idic(Y)(q11.2)(DYZ3+++/2)/46,X,+mar.ish idic(Y)(q11.2)(DYZ3+++/45,X, respectively. Gonads did not respond to hMG stimulation, while the administration of hCG increased testosterone secretion from 13.7 to 617 ng/dl (Table). Cystourethroscopic examination identified a uterine structure, which was laparoscopically removed at one year of age. Hypo- spadias was repaired and bilateral testicular biopsy was performed at two years of age. Biopsy specimens presented with germ cells and Sertoli cells in premature seminiferous tubules, and undifferentiated stroma, the findings being almost immature testis as seen in a prepubertal boy (Fig. 2b).

Zygosity Analysis by Allelotyping

Parent-child transmission of alleles was analyzed in the twins and their parents, using 22 highly polymorphic microsatellite markers that were selected
Table 1. Endocrinological Examination

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<td></td>
<td>(mIU/ml)</td>
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<td>30 min</td>
<td>60 min</td>
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<tr>
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<td>280</td>
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<tr>
<td>Twin 2 LH</td>
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<td>7.47</td>
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<td>2nd day</td>
<td>3rd day</td>
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<tr>
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<td>&lt;5.0</td>
<td>&lt;5.0</td>
<td>&lt;5.0</td>
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<tr>
<td>Twin 2</td>
<td>13.7</td>
<td>209</td>
<td>418</td>
<td>617</td>
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![Sexual organs of Twin 2. Scrotal hypospadias (a), and representative prepubertal immature testis (b) (Original magnification: × 200).](image)

from 22 autosomes. As a result, allelotypes at all the 22 loci were identical between the twins, indicating the affirmative probability for identical twins was 0.999999994. Parentage was also confirmed.

**Discussion**

Monochorionic, monozygotic twins of discordant sexual phenotype with sex chromosome mosaicism were herein reported. One (Twin 1) of the twins had female genitalia with minimal clitoromegaly, severely
dysgenetic testes and oviducts, while the other (Twin 2) had male genitalia with well-developed scrotum and immature testes. They would be diagnosed as the MGD variant in the dysgenetic male pseudohermaphroditism [2]. Gonadal dysgenesis in this entity varies from almost normal testis in which a full complement of Y chromosome is required to streak gonad as the most severe expression of faulty testicular differentiation [6, 7]. These twins showed mosaicism and its marker chromosome containing sequences of the Y chromosome. They were clinically monorchionic and their monozygosity was confirmed by allelotyping with microsatellite markers.

Until now 8 cases with monozygotic twins of discordant sex have been reported [5, 8]. Seven pairs of 8 cases had sex chromosome mosaicism and in one case, they had 46,XY karyotypes without any mosaicism in blood lymphocytes. All socially male twins were described as a normal male [8]. The male twin of no mosaicism case was born with hypospadias and affected with subfertility after puberty [5]. No complete correlation was documented among the mosaicism of sex chromosome, testicular differentiation, androgen production and the ultimate genital phenotypes in these cases. In our case, the ratio of chromosomal mosaicism, gonadal histology and testosterone productivity are reasonably correlated to individual genital phenotypes. The mosaicism in the peripheral lymphocytes may not reflect the same proportion of chromosome Y component of the gonads in one individual [9]. The use of buccal smear cells for chromosome analysis may have the advantage to confirm the mosaicism in our cases. Theoretically, the different proportion of mosaicism of gonads would result in various faulty gonadal differentiation independently in each twin.

The coarctation of aorta and the other Turner stigmata were present in Twin 1 of our case. The proportion of existence of Y component and 45,X cell line in buccal smear would reflect an individual sex differentiation in these twins. This is supported by the notion that the predominance of 45,X cell line in sex chromosome mosaicism manifest more Turner stigmata [10, 11].

The persistence of Müllerian component and incomplete masculinization of the internal and external sexual organs clinically ensures absent or insufficient secretion of Müllerian inhibitory substance and androgen in the dysgenetic testis, respectively. Thus, poor development of the Wolffian duct is consistent with the streak-like gonads and the lack of androgen secretion in Twin 1. On the other hand, the intrascrotal testis in Twin 2 brings may reflect appropriate development of the seminal tract, except for the Müllerian remnant, indicating the sufficient androgen secretion but the Sertoli cell failure.

In conclusion, we reported monozygotic twins with discordant sexual phenotypes due to different ratios of mosaicism of 47,X, idic(Y), idic(Y)/46,X, idic(Y)/45, X.

References

