Case Study

A rare case of 47,XXY/46,XY mosaic klinefelter syndrome with unique phenotype

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Klinefelter syndrome (KS) is one of the most common congenital chromosomal abnormalities and one of the most common causes of infertility in men. As there are mosaic forms (eg. 47,XXY/46,XY; 47,XXY/46,XX), there are also non-mosaic forms (eg. 47,XXY; 48,XXY; 49,XXXXY; 48,XXYY) of the disease. Although the clinical findings are variable, the mosaic forms have milder phenotype than non-mosaic forms. In addition to common features, some rare findings such as Persistent Mullerian Duct Syndrome, micropenis, cryptorchidism, and hypospadias may accompany the disease. We report here a 27-year-old male 47,XXY/46,XY (80%/20% respectively) mosaic type KS patient with unusual abnormalities like scrotal hyperpigmentation and evident intellectual disability as well as known ones and discuss it in the context of the literature.

Keywords: Klinefelter syndrome, mosaicism, persistent mullerian duct syndrome, scrotal hyperpigmentation.

INTRODUCTION

Klinefelter syndrome (KS) is a common congenital numerical anomaly of the sex chromosomes with an incidence of 1-2/1000 (Nieschlag, 2013). 47,XXY karyotype is the most common form with 80% and the rest 20% consists of mosaic forms (eg. 47,XXY/46,XY; 47,XXY/46,XX) and other variants (eg. 48,XXY; 49,XXXXY; 48,XXYY) (Nieschlag, 2013). 47,XXY/46,XY mosaicism affects 10% of all KS cases (Mohd Nor and Jalaludin, 2016). These abnormalities are caused by non-disjunction in cell cycle. The cases originated from maternal oogenesis cover almost two-thirds and the others originated from paternal spermatogenesis take over the remaining third (Nieschlag, 2013; Velissariou et al., 2006). Furthermore, the causes of sex chromosome mosaicism can be chimerism, loss of Y chromosome in some cells, double fertilization, and fusion of the twin embryos or fusion of the embryo with a polar body. As a result of the distribution of the different cell lines, the clinical findings of patients change (Velissariou et al., 2006).

KS affects only males with a large spectrum of signs and symptoms among patients (Groth et al., 2013). It can be said that there are four possible genetic mechanisms to clarify the differences between phenotypes: 1) degree of mosaicism, 2) variations in genes on the X chromosomes, 3) imprinting differences, and 4) gene dosage of X chromosome genes. Due to the imprinting status and gene dosage, parent of origin and the number of the extra X chromosomes and X inactivation of genes are important.
(Boada et al., 2009; Geschwind et al., 2000). The extra X chromosome interrupts male sexual development and causes low levels of testosterone (Bojesen et al., 2003). The severity of the disease is believed to be milder in mosaic forms than non-mosaic forms likely other chromosomal anomalies such as Turner syndrome (Doğer et al., 2015; Mohd Nor and Jalaludin, 2016). In contrast, the clinical findings of the disease, especially neurological findings, are more severe as the number of extra X chromosomes increases (Boada et al., 2009; Gropman and Samango-Sprouse, 2013). The peak range of age at diagnosis is the second decade and approximately 70% of patients are diagnosed before the age 20 (Pacenza et al., 2012b).

Major abnormalities seen in KS are infertility (91-99%), azoospermia (>95%), small testes (>95%), cryptorchidism (27-37%), high gonadotropin and low testosterone levels (>95%) which lead to decreased facial and pubic hair (60-80%), gynecomastia (38-75%), learning difficulties (>75%) and speech delay (40%), increased height (30%) and less often micropenis (small penile size) (10-25%), congenital malformations (eg. cleft palate) (18%), type 2 diabetes mellitus (10-39%), osteoporosis and fractures (10%), hypospadias, some cancers such as breast cancer (Groth et al., 2013). The incidence of infertility in KS patients due to severe azoospermia is approximately 90% in non-mosaic forms and 75% in mosaic forms (Mau-Holzmann UA, 2005). Some techniques which are most effective in adolescents after the onset of puberty such as testicular sperm extraction, intracytoplasmic sperm injection, in vitro fertilization, and Spermatogonial Stem Cell Banking may be used for the fertility preservation (Fullerton et al., 2010; Krausz and Chianese, 2014; Van Saen et al., 2012).

Persistent Mullerian Duct Syndrome (PMDS) is a rare male sexual development disorder including Mullerian duct derivatives, uterus, fallopian tubes and upper vagina, in a genotypically 46,XY normal male. Although a normal man possesses only Wolffian structures, a PMDS patient possesses both Wolffian and Mullerian duct derivatives. It is not a common occurrence for these abnormalities to exist in a mosaic KS patient at the same time (Rehman et al., 2008). Skin hyperpigmentation in genital region or scrotum is an early finding of congenital adrenal hyperplasia (CAH) leading to adrenal insufficiency. Due to the adrenal insufficiency, adrenocorticotropic hormone (ACTH) levels increase and lead to hyperpigmentation (Auron and Raissouni, 2015; Speiser et al., 2010). As far as we know, the genital hyperpigmentation with KS has not been reported previously.

**Case report**

A 27-year-old male patient was consulted to our clinic with an indication of micropenis. His parents were not consanguineous and he had three healthy siblings. In his medical and family history, there was not any specific finding related with this condition or other genetic diseases. Only important history was that according to patient’s parents, the school success was very bad and he had not spoken very well. His height was 180 cm and his weight 90 kg. Physical examination revealed no palpable testis in the scrotum, a penis with small size, mild hypospadias, genital hyperpigmentation, gynecomastia, decreased facial, axial and body hair (Figure 1). Importantly he did not cooperate and he could not understand and answer our questions and instructions. So he had an evident intellectual disability.

The laboratory studies showed elevated follicle stimulating hormone and luteinizing hormone levels and low testosterone levels (Table 1). We assessed adrenocorticotropic hormone and 17-OH progesterone levels and blood electrolytes to exclude CAH and these were in normal levels. The scrotal USG and abdominal MRI revealed that there was no testicular tissue in the scrotum, both inguinal canals and intraabdominal space, but there were hypoplastic cervix and upper vagina posterior to bladder (Figure 2). For cytogenetic studies, chromosome analysis was performed in peripheral blood using the GTG banding technique. One hundred cells were studied. The result was mosaic 20% 47,XXY and 80% 46,XY. All of these findings suggested that the most probable diagnosis was mosaic Klinefelter syndrome with persistent Mullerian duct syndrome, cryptorchidism, micropenis, hypospadias, genital hyperpigmentation and evident intellectual disability. We recommended diagnostic laparoscopy to the patient for exploration of testis tissue, however, his family refused to surgery. Thus, we couldn’t perform further treatment.

**DISCUSSION**

Klinefelter syndrome is one of the most common congenital chromosomal abnormalities and one of the most common causes of infertility in men. Because of relatively indistinct phenotype, diagnosis of KS patients in early ages may be missed and generally common complaints of most of the KS patients are azoospermia and infertility during second to fourth decade of life (Høst et al., 2014; Nieschlag, 2013; Pacenza et al., 2012b). Phenotypes of KS patients are variable and the mosaic ones have relatively milder phenotype and usually, the complaints consist of infertility and behavioral disturbances only (Boada et al., 2009; Mohd Nor and Jalaludin, 2016).

Only a few cases of PMDS with mosaic and non-mosaic KS were reported previously. To the best of our knowledge, eight cases of PMDS with 47,XXX/46,XX mosaicism and only one PMDS with 47,XXX/46,XY mosaicism exist in the current literature. When we reviewed the previous cases, we identified that KS patients with 47,XXX/46,XX mosaicism had similar mild phenotypes and ages, but
**Figure 1:** Photos of the patient. Gynecomastia and dysmorphic body structure (a); genital hyperpigmentation and cryptorchidism (b); micropenis and hypospadias (c) can be seen.

**Table 1.** Baseline hematological, biochemical and hormonal characteristics of the patient

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Results</th>
<th>Normal Ranges</th>
</tr>
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<tbody>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>13.6</td>
<td>11-16</td>
</tr>
<tr>
<td>White cell count (10^9/L)</td>
<td>6.4</td>
<td>4-10</td>
</tr>
<tr>
<td>Platelet count (10^3/uL)</td>
<td>229</td>
<td>100-400</td>
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<tr>
<td>Serum creatinine (mg/dl)</td>
<td>0.7</td>
<td>0.1-1.2</td>
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<tr>
<td>Serum sodium (mmol/L)</td>
<td>140</td>
<td>135-146</td>
</tr>
<tr>
<td>Serum potassium (mmol/L)</td>
<td>4.3</td>
<td>3.5-5.1</td>
</tr>
<tr>
<td>FSH (mIU/ml)</td>
<td>16.8</td>
<td>1.5-12.4</td>
</tr>
<tr>
<td>LH (mIU/ml)</td>
<td>13.12</td>
<td>0.55-12.05</td>
</tr>
<tr>
<td>Total serum testosterone (ng/ml)</td>
<td>2.36</td>
<td>2.84-8</td>
</tr>
<tr>
<td>ACTH (pg/ml)</td>
<td>24.6</td>
<td>0-46</td>
</tr>
<tr>
<td>17-OH progesterone (ng/ml)</td>
<td>0.63</td>
<td>0.45-2.15</td>
</tr>
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ACTH: adrenocorticotropic hormone

FSH: follicle stimulating hormone

17-OH progesterone: 17-hydroxyprogesterone

LH: luteinizing hormone

differently only one patient had ovarian tissues, and the patient with 47,XXY/46,XY mosaicism had also similar phenotype but older age of 58 (Crooke and Hayward, 1960; Delaney et al., 2004; Ford et al., 1959; Hetch et al., 1966; Matsuki et al., 1999; Mohd Nor and Jalaludin, 2016; Nowakowski et al., 1960; Rehman et al., 2008; Song et al., 2016;.)
Figure 2: Abdominal MRI of the patient Penile tissue (red arrow;a), hypoplastic cervix (red thin arrow;b and red arrow;c) and upper vagina posterior to bladder (red thick arrow;b and red star;c) were revealed

2014; Velissariou et al., 2006). In addition, in the literature, there is no case of PMDS with micropenis, hypospadias, and cryptorchidism related with KS. Apart from being rare, micropenis, hypospadias, and cryptorchidism may be with KS; however, evident intellectual disability and genital hyperpigmentation are not commonly seen in KS patients (Groth et al., 2013; Nieschlag, 2013). KS patients have some neurological findings such as learning difficulties, behavioral disturbances such as nervousness, anxiety and rarely schizophrenia, but these neurological abnormalities are usually slight (Boada et al., 2009). Though there is not an IQ testing of our patient, there is no doubt he had evident intellectual disability due to his apathy, difficulty in understanding and answering very low school success and also according to his family. Genital hyperpigmentation is seen in some ambiguous genitalia cases which are usually related to different forms of CAH and adrenal insufficiency and could go with some genital anomalies such as hypospadias, cryptorchidism, inguinal hernia, and early and excessive hirsutism etc. Hyperpigmentation is an early sign of CAH in male neonates. CAH is most commonly caused by 21-hydroxylase deficiency which is a genetic disease leading to salt wasting and for diagnosis in addition to clinical findings, ACTH, 17-OH progesterone and serum electrolyte levels, and mutation analysis of CYP21A2 gene can be done (Auron and Raissouni, 2015; Speiser et al., 2010). Because our patient suffered from hypospadias, cryptorchidism, micropenis, and hyperpigmentation, to exclude co-existence of KS and CAH, we tested ACTH, 17-OH progesterone, and serum electrolyte levels initially and found them in normal levels. Consequently, despite the fact that the mosaic KS patients are expected to have milder phenotype, our patient’s signs and symptoms are more severe when compared to previous reports of mosaic KS cases. And also the co-existence of persistent Mullerian duct syndrome, cryptorchidism, micropenis, hypospadias, genital hyperpigmentation and evident intellectual disability in a mosaic KS patient was a unique association.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of the paper.

REFERENCES

Crooke AC, Hayward MD (1960) Mosaicism in Klinefelter’s
Syndrome. Lancet 275