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□ 증례 □

A Case of Swyer Syndrome

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－Abstract－

46,XY pure gonadal dysgenesis is a sex-reversal disorder, that is characterized by the presence of a female phenotype, with a normal to tall stature, primary amenorrhea and sexual infantilism. The internal genitalia are female with a uterus and vagina being present, however, there are bilateral dysgenetic gonads. In addition, neoplasia occurs in 20～30% of patients who have gonadal dysgenesis and a Y chromosome. A 34 year old woman presented to our hospital with the chief complaint of primary amenorrhea. Physical examination revealed no secondary sexual characteristics and no somatic abnormality. Peripheral blood karyotype was 46,XY, and polymerase chain reaction (PCR) for the Sex determining Region Y (SRY) gene was positive. Sequencing analysis of the SRY gene revealed a single nucleotide polymorphism. A laparoscopic gonadectomy was performed to remove both gonads, and no tumor cells were observed. Estrogen replacement therapy was instituted.

Key Words : Swyer syndrome, SRY gene, Gonadal dysgenesis

Introduction

46,XY pure gonadal dysgenesis, also known as Swyer syndrome, is an uncommon disorder of sexual differentiation that is characterized by the presence of a female phenotype, primary amenorrhea, sexual infantilism and bilateral streak gonads without the somatic abnormality of Tuner's syndrome.[1] This condition may occur sporadically or be inherited as an autosomal recessive trait or be inherited as an X-linked trait in XY gonadal dysgenesis.[2] As many as 20～30% of patients with this condition are at the risk for the formation of gonadal tumors, therefore patients should undergo

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Table 1. Sequences of primers using polymerase chain reaction and direct sequencing of the SRY gene

	Primer sequences	Size of products
Forward primer	*5′-TTTCGAACTCTGGCACCTTT-3′*	739 bp
Reverse primer	*5′-AAAGTGAGGGCTGTAAGTTATCG-3′*	

SRY; Sex determining Region Y

prophylactic gonadectomy soon after diagnosis.[3] We report here a case of Swyer syndrome with a brief review of literature.

Case report

A 34-year-woman presented to our hospital complaining of primary amenorrhea. Approximately 15 years earlier, she had been informed that she had a constitutional chromosomal abnormality, however she took no medical treatment at that time. When she presented at our hospital, she had a normal stature, scanty pubic and axillary hair, no breast development, and female external genitalia. A gynecological examination of the internal genitalia showed the presence of a normal uterus and vagina. Pelvic MRI revealed female internal genitalia with a small sized uterus and full vagina, but neither ovaries nor testes were detected. A hormonal profile revealed decreased estradiol levels (<10 pg/ml), elevated follicle stimulating hormone (FSH) levels up to 80.12 IU/L (reference range ; 0-25 IU/L) and luteinizing hormone (LH) levels up to 20.75 IU/L

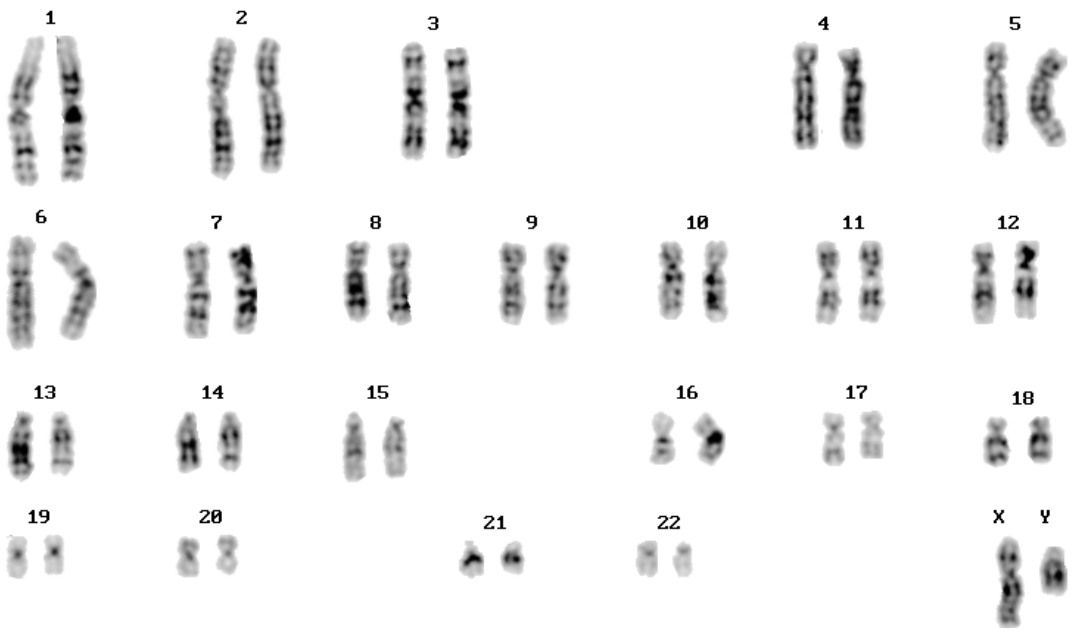

Fig. 1. The representative karyotype shows 46,XY.

(reference range ; 0-20 IU/L). Testosterone level was 0.12 ng/ml (reference range for women ; <0.8 ng/mL) and prolactin level was 18.73 ng/ml (reference range for women ; 1-25 ng/mL). Cytogenetic analysis was performed using the peripheral blood T-lymphocyte, and the karyotype was 46,XY (Fig. 1). We designed a set of primers for amplification of the entire Sex determining Region Y (SRY) gene (Table 1). In polymerase chain reaction (PCR) for the SRY gene, a single band was detected in 739 bp, as would occur for a normal male (Fig. 2). Direct sequencing of PCR product, revealed that the cytosine at nucleotide position 465 altered to thymine, but the serine at amino acid position 155 was not changed by this nucleotide alteration, indicating that single nucleotide polymorphism (SNP) had occurred. Laparoscopic salpingectomy and gonadectomy was carried out and the histological examination of the gonad like lesions was consistent with gonadal dysgenesis, however no tumor cells were found. Estrogen replacement therapy was started.

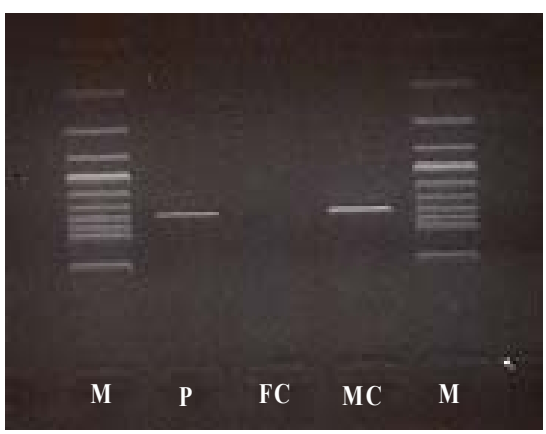

Fig. 2. Single band was detected in 739 bp in polymerase chain reaction for the SRY gene. SRY; Sex determining Region Y, M; size marker, P; patient, FC; female control, MC; male control

Discussion

46,XY gonadal dysgenesis is characterized by abnormal testicular determination,[4] and the form of gonadal dysgenesis is determined based on the histology of the affected gonad.[5] Individuals with 46,XY pure gonadal dysgenesis (Swyer syndrome) lack testicular development and have bilateral streak gonads.[6] Because they do not have testes, testosterone and antimullerian hormone (AMH) are not produced. The Wolffian structures (seminal vesicles, vas deferens and epididymis) fail to develop due to lack of testosterone, however the Mullerian structures (uterus, fallopian tubes and upper third of the vagina) develop well without AMH. Individuals with 46,XY mixed gonadal dysgenesis have a streak gonad on one side and dysgenetic or normal appearing gonad on the other side.[6, 7] Swyer syndrome, first described by Swyer in 1955, is a rare syndrome characterized by a female phenotype, normal to tall stature, eunuchoid with normal female external genitalia, hypoplastic uterus and fallopian tubes, bilateral dysgenetic gonads and sexual infantilism with primary amenorrhea.[8]

The first step in the sexual differentiation

of a normal XY fetus is the testicular development. The early stage of testicular formation in the second month of gestation requires the action of several genes, of which one of the earliest and most important is the SRY gene. If the SRY gene absent, the fetal gonads develop as ovaries. In addition, the SRY gene plays a essential role in sex determination and testicular development. It is located on the short arm of the Y chromosome (Yp11), and consist of a single exon in which the central area of the open reading frame (ORF) encodes a 79-amino-acid region with high similarity to a motif known as the high-mobility-group (HMG) box.[9] HMG-box-containing protein has DNA-binding and DNA-bending activities and acts as a transcriptional regulator. Altered SRY sequence has been reported in 15~20% of the cases of 46,XY gonadal dysgenesis,[10] most of which occur in the HMG box, leading to alteration of the DNA-binding and DNA-bending activity, which is essential in the induction of testicular development by the SRY protein.[11] However, mutation of the SRY gene has not detected in many patients with Swyer syndrome, including the one evaluated in our case. Therefore, there may be another unknown genetic locus that is involved in the testicular development. To date, two other chromosomal regions have been implicated in XY sex-reversal without additional malformations: the subtelomeric region of the short arm of chromosome 9 and the dosage sensitive sex reversal (DSS) locus on the short arm of the X chromosome.[12]

Germ cell tumors, including gonadoblastoma and dysgerminoma, occur in 20~30% of the patients who have gonadal dysgenesis and the Y chromosome. The presence of mutations in the SRY gene is highly related to the presence of germ cell tumors in pure XY sex-reversal patients,[13] however a recent study described an XY female with dysgerminoma and no mutation in the coding region of the SRY gene.[14] The results of these reports suggest that SRY is one of several genes involved in the initiation of gonadal neoplasm, and detection of mutations in the SRY gene alone cannot predict the presence of gonadal tumors. In addition, it seems that the presence of a malignancy is related to the age of the patient. The incidence of germ cell tumors increases to 50~70% in the third decade of life and to 80% at 40 years of age. The increasing incidence suggests that additional mutations of genes other than SRY occur with advancing age.[15]

Patients diagnosed with Swyer syndrome should undergo prophylactic bilateral gonadectomy, followed by estrogen replacement therapy, which can induce secondary sexual characteristics.

요 약

46,XY 순수 생식선 이형성증은 여성의 표현

형에 정상 혹은 큰 키를 가지며 원발성 무월경과 성적 유치증을 보이고, 내부 생식기에 자궁과 질이 존재하지만 양측 성선 이형성을 나타내는 성전환(sex-reversal)질환의 일종이다. 성선 이형성증과 Y 염색체를 가자는 환자의 20~30%에서 종양이 발생한다. 이차 성징이 결여되어 있고 그 외의 다른 신체적 기형은 발견되지 않은 34세 여성이 원발성 무월경을 주소로 내원하였다. 말초혈액 핵형분석에서 46, XY였고, 중합효소 연쇄반응(Polymerase Chain Reaction)에서 SRY(Sex Detetmining Region Y) 유전자 양성으로, SRY 유전자 염기서열 분석에서는 단일 염기 변이를 보였다. 복강경을 이용한 양측 성선제거술을 시행하였으며, 종양세포는 발견되지 않았다. 수술 후 에스트로겐 대체 요법을 시행하였다.

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