Feminizing Genitoplasty for Treatment of XX Male with Masculine Genitalia

Masakazu Kurita, M.D.
Emiko Aiba, M.D.
Daisuke Matsumoto, M.D.
Katsujiro Sato, M.D.
Takashi Nagase, M.D.
Kotaro Yoshimura, M.D.
Tokyo, Japan

XX male is a kind of sexual differentiation disorder that affects one out of every 20,000 to 25,000 male births. The patients have male phenotypes with female chromosomes, the karyotype 46XX. More than 150 XX males have been reported in the medical literature since Albert de la Chapelle first reported a male human with a pure XX sex chromosome constitution in 1964.[1,2] Most patients with this condition have fully developed masculine genitalia with or without testes, and sexual ambiguity is rarely seen. Usually, patients appear male, are brought up as male, and have male orientation psychosexually. The hypothetical Y chromosomal gene(s) responsible for testis determination was named *TDF*, for testis determining factor, and later a crucial gene was identified on the human Y chromosome and termed *SRY*, for sex-determining region Y.[3] It is said that sex reversal leading to testes in XX males is most often due to the presence of the *SRY* gene.[4] The abnormality may arise during meiosis in the father, when an abnormal exchange leads to the transfer of the entire pseudoautosomal region plus a portion of the Y chromosome–specific region (including *SRY*) onto the X chromosome. However, advances in molecular genetics revealed another type of mechanism leading to XX sex reversal,[5] and the etiology of this type of sexual differentiation disorder may be heterogeneous. We present the rare case of an XX male patient who was eager to live as a female and underwent surgery corresponding to a male-to-female transsexual operation (resection of the penis, repositioning of the urethra, and vaginal construction). As far as we know, this is the first report of an XX male patient who underwent feminizing genitoplasty.

From the Department of Plastic Surgery, University of Tokyo School of Medicine.
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CASE REPORT

A 39-year-old woman presented with masculine external genitalia but no testes in the scrotum. She was born with masculine external genitalia with an empty scrotum and was brought up as a male. At age 4, she underwent surgery in a urology department under the diagnosis of cryptorchidism (undescended testicles). At the age of 27, the patient was diagnosed as schizophrenic by a psychiatrist and took a kind of major tranquilizer. Afterward, she was tormented by enlargement of the breasts; this time, she was diagnosed as having severe gynecomastia. She was referred to an endocrinologist, an extensive work-up was performed, and her sex chromosome was found to be 46XX, consistent with the normal female karyotype.

According to the patient, since her chromosomal sex proved to be that of a woman, she started to complain about her legally registered sex and her male appearance, and wished to change both from male to female. She underwent bilateral castration at a clinic when she was 31 years old. After careful consideration of her request, along with the results of medical examinations, such as sex chromosome tests, the court officially permitted the alteration of her registered sex when she was 38 years old. Three months after hormone replacement therapy was begun by a psychiatrist, she visited our department in hopes of undergoing feminizing genitoplasty.

She had a small but mature penis with no mass palpable in the scrotum. Surgical scarring found in the pubic region was due to the operation performed for cryptorchidism at age 4 (Fig. 1). No gonads or remnants were found in the course of inspection by computed tomography and magnetic resonance imaging. To confirm her chromosomal sex, fluorescence in situ hybridization was performed, and the result of chromosomal analysis demonstrated 46XX. Serum hormonal analysis showed a follicle-stimulating hormone level of 22.9 mIU/ml (female/male normal range, 9.2 to 124.7/1.6 to 10.6 mIU/ml), a luteinizing hormone level of 6.6 mIU/ml (range, 7.5 to 56.2/1.8 to 9.1 mIU/ml), an estradiol level of 9.9 pg/mg (range, 16 to 331/16 to 71 pg/mg), and a testosterone level of 0.2 ng/dl (range, 16 to 86/277 to 1111, ng/dl) under the treatment of oral conjugated estrogen (3.75 mg per day).

Feminizing genitoplasty was performed with our modification of the technique described by Rehman and Melman[6] (Figs. 2 and 3). Inverted penile skin was used to construct a neovagina, and a neoclitoris was constructed with a small dorsal part of glans elevated as an island flap with a neurovascular bundle. Peritoneal and scrotum incisions were made as shown in Figure

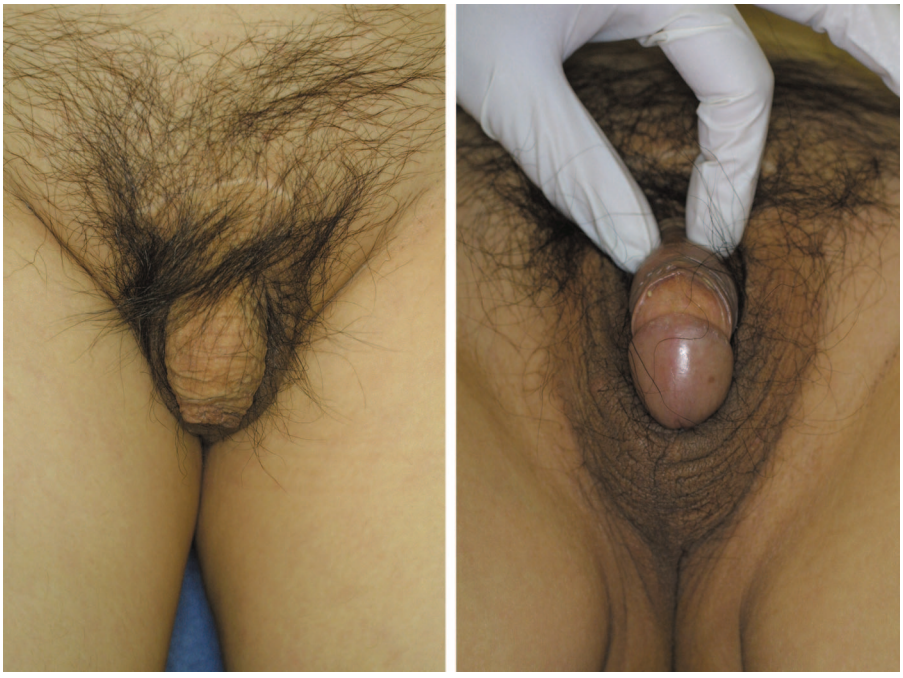

Fig. 1. Appearance of external genitalia before surgery. The patient had a small but mature penis, with no testes palpable in scrotum. A surgical scar can be seen in the pubic region.

2, and part of the scrotal skin was used as a patched skin graft by suturing it on the distal end of the inverted penile skin flap to make the neovagina deeper. To make labia majora, divided scrotal skin flaps were advanced posteriorly (Fig. 4).

Though she was bothered by incontinence during the first 2 weeks after surgery, no urine leakage or stricture of the urethra took place after that. Two years have passed since the operation, and the cosmetic appearance of the operative site is satisfactory. The neovagina has smooth walls, and no vaginal obstruction was seen on dilation with a 50-cc syringe. The neovagina was 12 cm deep and 3 cm in diameter. We cannot report on her sexual functionality, especially with regard to sensation, because the patient has not engaged in sexual intercourse since the procedure was completed. The patient is living daily life as a female and is content with the results (Fig. 5).

DISCUSSION

Analysis of XX male patients has permitted identification at the molecular level of some genes involved in sex determination, including *SRY*. This gene is the switch that starts male sexual differentiation by triggering the Sertoli cell lineage. Other genes involved in the process of sexual differentiation have been isolated, too.[4] In other words, the etiology of the condition is heterogeneous. XX sex reversal is divided into three subgroups[7] : 46,XX males with the *SRY* gene (the majority, at about 80 percent)[4] ; 46,XX males without the *SRY* gene; and 46,XX/XY mosaic. Our patient's sex chromosome was XX, as confirmed by in situ hybridization. Therefore, she would be included in the first or second group.

The clinical presentation of this condition varies. It is said that almost all individuals with the XX male condition show micro-orchidia with a normal-size penis. Signs of hypogonadism are frequent, with gynecomastia in half of the cases. These patients may seek medical advice because of infertility or short stature; others may present with hypospadias, anal fistula, or sexual ambiguity.[7] Our patient took a typical clinical course; she was first referred to an endocrinologist to determine the cause of the drug-induced breast enlargement (severe gynecomastia), a sign of hypogonadism. The symptoms in XX male patients are clinically indistinguishable from those of patients with Klinefelter's syndrome (47,XXY).[8] Chromosomal analysis is a way to differentiate between these conditions.

The patient had been suffering from schizophrenia, though her mental status was under good control by medication when she was admitted to our department. The combination of XX male and schizophrenia has been reported,[9,10] and psychoses have frequently been reported in patients with abnormal sex chromosome constitutions.[11]

Most XX males show abnormal hypothalamic gonadal axis function, with a lower than normal level of testosterone and increased follicle-stimulating hormone and luteinizing hormone levels.[12] In this case, we could not review her original hormone secretion profile because she had already been treated with oral

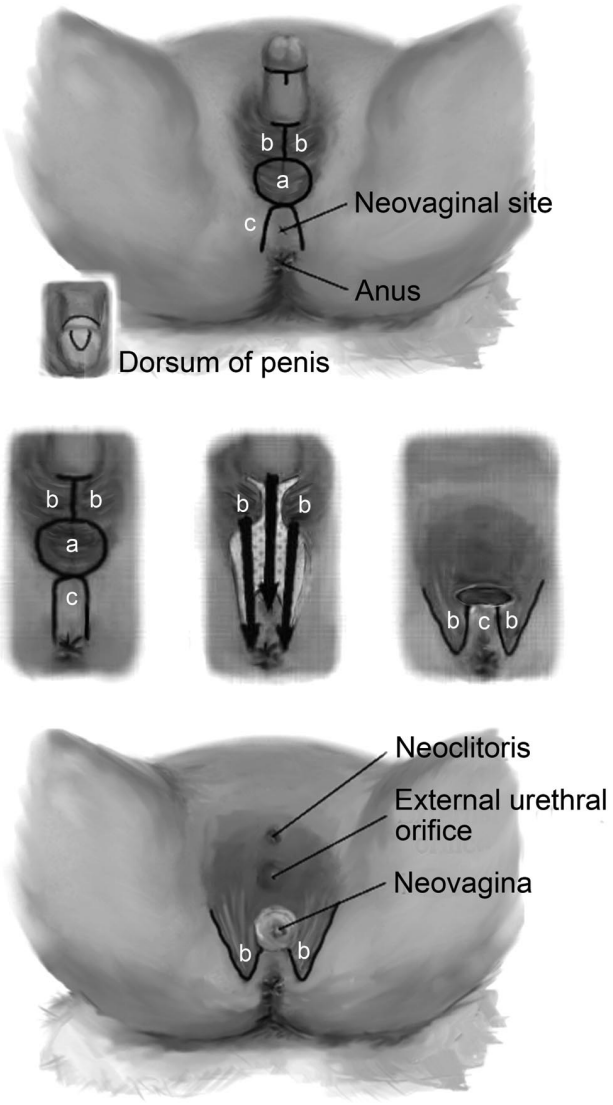

Fig. 2. (*Above*) A perineal skin incision was made, the penile skin flap was turned inside out, and a part of scrotal skin (*a*) was sutured as a skin graft to the bottom of the neovagina. (*Center* and *below*) The neovagina was constructed with the turnover penile skin flap, the scrotal skin graft was transposed to the space of the neovagina, and the scrotal skin flaps (*b* flaps) were advanced backward. The tip of the *c* flap was inserted into the posterior wall of the neovagina. Finally, an incision for the clitoris and urethra was made at the center of the penile skin flap.

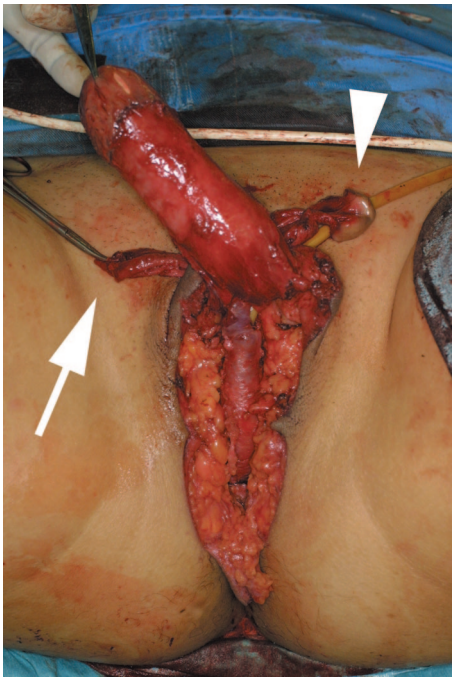

Fig. 3. View just before the turnover penile skin flap with a stent inserted was transposed into the neovagina space. A skin graft was sutured to the bottom of the neovagina. A small part of the glans was elevated as a neurovascular island flap for the neoclitoris (*arrowhead*). A part of the dissected penile cavernosum was also elevated and discarded afterward (*arrow*).

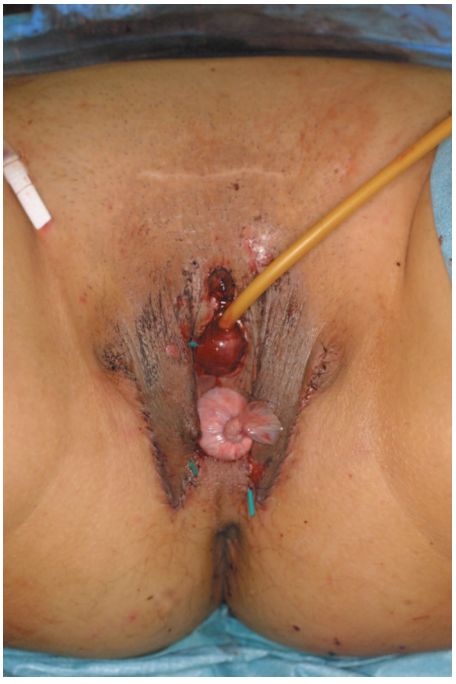

Fig. 4. View of the patient just after the surgery. A urethral catheter and intravaginal stent were left in the neourethral orifice and neovagina, respectively. The neourethral catheter was removed on day 8, and the stent was changed to new one on day 7. The patient was instructed to use the stent for 1 month.

conjugated estrogen. When treating ambiguous genitalia, such as that seen in patients with 46XX congenital adrenal hyperplasia, surgeons have to evaluate the anatomy of the external genitalia and the top of the vagina, because degrees of virilization vary.[13] This time, however, the patient had been classified as an XX male and had almost normal external genitalia, with the development of male sexual ducts but the absence

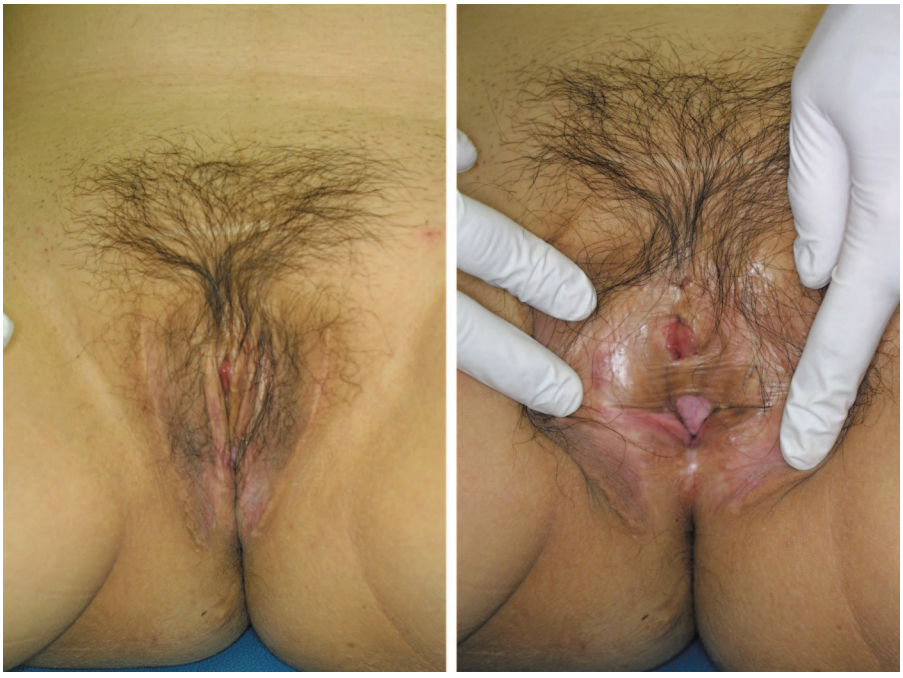

Fig. 5. Twelve months after operation. The neovagina has smooth walls and no vaginal obstruction is seen.

of testes. We performed an operative technique usually used in sex reassignment surgery. To compensate for the length of the penile skin flap, we used a scrotum skin graft at the bottom of the neovagina, which resulted in a constructed vagina with sufficient depth.

This patient had come to feel discomfort with her own gender, after she learned the facts about her chromosomal sex. She is the first documented XX male patient who wanted to live as a female and underwent feminizing genitoplasty. We adopted the procedure used in male-to-female transsexual surgery with satisfactory results.

In Japan, a family register system is used, and as in other countries, the registered sex is determined by the appearance of the external genitalia at birth. With regard to intersex conditions, the registered sex can be changed with judicial consent. During the process, chromosomal, gonadal, and hormonal sex and genitalia after development and plastic surgery, if performed, are taken into consideration. In this case, chromosomal sex was probably the deciding factor. In July of 2004, the law permitting gender identity disorder patients to change their legal sex was enacted, so surgical treatment of adult genitalia may possibly be in demand in the future.

SUMMARY

XX male is a rare condition. Usually, the patient is brought up and mentally orientated as a male. We encountered an XX male patient eager to live as a female, the first documented case, and performed feminizing genitoplasty. Because of the patient's fully developed external genitalia, we adopted the procedure usually used in male-to-female transsexual surgery. No major complications have been seen, and the patient is pleased with the functional and aesthetic results.

Kotaro Yoshimura, M.D.
Department of Plastic Surgery
University of Tokyo School of Medicine
7-3-1 Hongo Bunkyo-ku
Tokyo 113-8655, Japan
yoshimura@cosmetic-medicine.jp

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