

## Testicular feminization: complete androgen insensitivity syndrome. Discussions based on a case report

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### Abstract

**Introduction and Objectives:** Testicular feminization is the syndrome when a male, genetically XY, because of various abnormalities of the X chromosome, is resistant to the actions of the androgen hormones, which in turn stops the forming of the male genitalia and gives a female phenotype. The androgen insensitivity syndrome occurs in one out of 20 000 births and can be incomplete (various sexual ambiguities) or complete (the person appears to be a woman). The aim of this paper is to present the diagnosis and treatment of a case of testicular feminization. **Patient and Methods:** A 22-year-old patient is admitted at Gynecology for primary amenorrhea. The clinical examination shows a female phenotype: the breasts are normally developed, but there is no hair in the groins and axillary areas, the labia are small and hypoplastic, the urinary meatus is normally inserted, and the vulva is unpigmented. The gynecological exam reveals that the hymen is present, the vagina has 1.5 cm in length, while the uterus is absent. At Endocrinology, the levels of gonadotropins were measured and found normal (FSH 3.18 mU/mL, LH 15 mU/mL), the progesterone was 5.79 nmol/L, estradiol was 82.39 pmol/L and the testosterone was 4.27 nmol/L. The karyotype was mapped in order to differentiate the androgen insensitivity syndrome from other genetic abnormalities, like the Klinefelter syndrome (46XXY), Turner syndrome (45XO), mixed gonadal dysynergia (45XO/46XY) or tetragametic chimerism (46XX/46XY). These tests confirmed the suspected diagnosis – testicular feminization (46XY). The pelvic CT scan revealed the lack of uterus and ovaries, hypoplastic vagina, and intra-abdominal prepubertal testes. The testes were removed in order to avoid the malignant risk. We performed laparoscopic bilateral orchiectomy. **Results:** Surgically, the patient had a simple evolution, being discharged in the second day postoperative, and estrogen therapy was started from that moment on. Mentally, the patient kept thinking she was a woman, so the decision of telling her the truth was left to the parents. **Conclusions:** Testicular feminization is a rare disease that must be diagnosed and treated through close work between gynecologists, endocrinologists, geneticists, urologists, and psychiatrists. Bilateral laparoscopic orchiectomy is the best procedure to remove the intra-abdominal testes, in order to avoid their malignant transformation.

**Keywords:** testicular feminization, androgen insensitivity syndrome, testosterone, laparoscopic orchiectomy.

### ☒ Introduction and Objectives

Testicular Feminization, or the Androgen Insensitivity Syndrome, is a rare disease when a male, genetically XY, because of various abnormalities of the X chromosome, has some physical characteristics of a woman, or even a full female phenotype.

The aim of this paper is to present the diagnosis and treatment of a case of Complete Androgen Insensitivity Syndrome, and the discussions that follow it.

Androgen Insensitivity Syndrome occurs as the genetic defects determine a resistance to the actions of the androgen hormones, which in turn switches the development towards the aspect of a woman. The Androgen Insensitivity Syndrome is seen in one out of 20 000 births and can be incomplete (various sexual ambiguities) or complete (female phenotype). This disease had been suspected for hundreds of years, but significant progress in understanding it has been made since the 1950s, beginning with the work of Lawson Wilkins [1].

During the 6<sup>th</sup> week of the male fetal development, under the influence of the SRY gene located on the Y chromosome, the testes begin to differentiate from the genital ridges at the medial posterior abdominal cavity.

Leydig cells appear through the end of the 8<sup>th</sup> week, and they start producing testosterone. Afterwards, under the influence of androgen hormones, the rest of the male sexual characteristics slowly take place (including the testicular translocation to the scrotum). But, in the absence of testosterone female sexual characteristics develop [1].

Testosterone affects cells through androgen specific nuclear receptors, proteins encoded by a gene located on the proximal long arm of the X chromosome, specifically locus Xq11-Xq12. This gene has approximately eight exons, which translates into 919 codons, or 2757 nucleotides. Until 2010, more than 400 mutations of this gene have been discovered and they are either inherited from the mother, in an X-linked recessive pattern, or *de novo* spontaneous mutations (mutations in the germ cells from the parents' gonads or in the egg cell) [1].

However, not all mutations result in a defective androgen receptor. This protein comprises of several functional parts: the transactivation domain, the DNA-binding domain, the hinge, and the steroid-binding domain. In addition, most likely the transactivation domain, which represents more than half of the receptor, is affected. This translates in an inability of all cells to recognize and use testosterone, thus leading to Androgen Insensitivity Syndrome [2].

But, there are cases of Testicular Feminization that occur without a mutated androgen receptor gene. Other much less frequent causes are: mutant steroidogenic factor-1 protein; a deficit in the transmission of a transactivating signal from the N-terminal region of the normal androgen receptor to the basal transcription machinery of the cell [3].

In a normal cell, testosterone enters, and under the influence of 5-alpha-reductase, it is converted to dihydro-testosterone. But, both hormones exert their effects after binding with the steroid-binding domain of the androgen receptor. After the binding, the receptor undergoes phosphorylation and conformational changes, which force it to translocate to the nucleus. There, the receptor is dimerized and binds with DNA, resulting in the transcription of the targeted genes [4].

Mutations can affect any of these stages, starting from the synthesis of the androgen receptor protein, and ending with the transcriptional ability of the dimerized complex and the effect is one of the various forms of Androgen Insensitivity Syndrome. It has also been speculated that minor mutations of the androgen receptor, in patients with a male phenotype, are involved in the development of breast cancer, prostate cancer, or spinal and bulbar muscular atrophy [2].

Mild Androgen Insensitivity Syndrome, which is associated with a (normal) male phenotype, is often undiagnosed, the various small abnormalities that occur being overlooked either by the patient or the doctor. It can be identified only if affected men have problems with fertility. Therefore, oligo-azoospermia and reduced secondary pilosity can imply the Androgen Insensitivity Syndrome. Other signs can be gynecomastia and hipospadias, and the serological levels of luteinizing hormone and/or testosterone can be elevated. However, genetic tests are needed at this point to finalize the diagnosis [5].

More severe forms of Incomplete Androgen Insensitivity Syndrome, with different degrees of genital ambiguity, are observed at birth. Immediately the concentrations of hormones like testosterone, dihydro-testosterone and human chorionic gonadotropin are determined. Also, the human chorionic gonadotropin stimulation test can be performed (testosterone levels increase after the administration of hCG). But, the diagnosis is still difficult, as Incomplete Androgen Insensitivity Syndrome can have normal (non-mutated) androgen receptor gene. Today the gold standard for this disease is studying the androgen binding in a genital skin fibroblast. Moreover, an abdominal ultrasound reveals the absence of the uterus, while CT scans can find undecided testes [6].

Finally, Complete Androgen Insensitivity Syndrome, with its female phenotype, is overlooked at birth, and is diagnosed at puberty, when the patient reports primary amenorrhea. But, can be found even prenatally if the karyotype is determined from the amniotic fluid, and the genetic sex is verified through ultrasound. However, this is rarely the case. Back to puberty, when the first thing to be done to assess the amenorrhea is to determine the

serologic levels of the various sexual hormones and out of the ordinary is an elevated testosterone. Clinical examination reveals a short vagina, and no uterus, and imaging techniques (ultrasound, CT, MRI) confirm the absence of the uterus and ovaries, and discover intra-abdominal undescended testes [7].

Afterwards the karyotype must be mapped, in order to differentiate the Androgen Insensitivity Syndrome from other genetic abnormalities, like the Klinefelter syndrome (46XXY), Turner syndrome (45XO), mixed gonadal dyssynergia (45XO/46XY) or tetragametic chimerism (46XX/46XY), and to find the mutated androgen receptor gene [8].

Treatment is always symptomatic, meant to resolve the effects of the genetic mutation.

Mild forms of Incomplete Androgen Insensitivity Syndrome usually require no treatment. Eventually, the gynecomastia and hypospadias can be surgically corrected and supplements of testosterone can correct infertility when it is caused by low sperm count, and induce the development of secondary sexual characteristics [9].

Other more severe forms of Incomplete Androgen Insensitivity Syndrome need harsher methods of treatment. First of all, the sex of the newborn must be carefully chosen, taking into consideration the potential for virilization and for fertility, the complexity of the reconstructive surgical procedure and the anticipated gender self image of the patient. Today, because of genetics and the presence of the testes, most kids are raised as males. But, approximately 25% of patients are unsatisfied with the assigned sex [10].

Then, a genitoplasty is needed in concordance with the chosen sex. This being an irreversible procedure though, can be postponed until the patient develops sexual awareness, around the age of three, and can help with the decision. Feminization surgery is generally easier, and has fewer urological complications. But, usually requires a second intervention, at puberty, to complete the phenotype. Feminization implies labiaplasty and vaginoplasty (with later vaginal dilatations), the separation of the urethra from the vagina, the reduction of the clitoris and, of course, orchiectomy (open or laparoscopic). Masculinization procedures include the reconstruction of the hypospadiac urethra, orchidopexy, straitening the curved penis and the removal of the remnant Müllerian ducts and an erectile prosthesis at puberty if so decided [10].

Hormonal supplements are later administered in accordance with the assigned sex, and the doses modulated to mimic the normal levels from the various stages of growth. Artificially induced puberty is indistinguishable from normal puberty. Last but not least, patients should undergo psychiatric counseling, to cope with all the changes [11].

The management of Complete Androgen Insensitivity Syndrome is a lot more simple, and consists of defining the almost normal female phenotype. Often vaginal dilatations are required, and always the intra-abdominal testes must be removed, to avoid the risk of cancer. Estrogens should be administered postoperative, as there

is no more testosterone to be aromatized and a psychiatrist should be on stand-by in case the truth is revealed to the patient [12].

**☒ Patient, Methods and Results**

A 22-year-old woman was admitted at a Gynecology Clinic for primary amenorrhea. After a quick clinical examination that revealed a female phenotype (the breasts were normally developed, but there was no hair in the groins and axillary areas, the labia was small and hypoplastic, the urinary meatus was normally inserted, and the vulva was unpigmented) a gynecological exam was performed and revealed a present hymen, a short vagina (1.5 cm in length), and no uterus (Figure 1).

The patient was referred to an Endocrinology Clinic for further tests. Here, sexual hormones in the blood were determined. Gonadotropins were measured and found normal (FSH 3.18 mU/mL, LH 15 mU/mL), the progesterone and estradiol had normal levels for a woman (5.79 nmol/L and 82.39 pmol/L), but the testosterone was 4.27 nmol/L, just like a boy at puberty.

With the help of a geneticist the karyotype was mapped, and was revealed to be normal 46XY. Androgen receptor gene- abnormality research and an androgen binding test in a genital skin fibroblast were not accessible. To help with the diagnosis of Complete Androgen Insensitivity Syndrome a pelvic CT scan was needed, and it revealed the lack of uterus and ovaries, hypoplastic vagina, and intra-abdominal prepsoic testes. Then a decision to remove the undescended testes was taken, to

avoid risk of malignancy. This was also based on the patient’s self-image, and the advices of a psychiatrist (Figure 2).

The patient was then referred to our Urology Clinic, for the surgical treatment. A laparoscopic approach was considered the best option, being a minimally invasive procedure with low associated morbidity. The orchiectomy was done in a dorsal decubitus, under general anesthesia. Three ports were needed, one 12 mm umbilical for the camera, and two 5 mm bilateral, on the midclavicular line below the level of umbilicus, for the scissors and the forceps. Carbon dioxide was insufflated through the umbilical port, until a pressure of 15–20 mmHg was obtained in the pneumoperitoneum. During the procedure, the testes were found inside the abdominal cavity, in the prepsoic region. They were subsequently dissected and removed. Carbon dioxide was then exufflated, and the fascia and the skin were sutured (Figures 3 and 4).

Postoperative evolution was uneventful; the patient was discharged after one day, and went back to Endocrinology for estrogen substitution therapy. Histopathology revealed two testes, with atrophy of the seminiferous tubules, insufficient development of the germinal cells with the persistence of the Leydig elements and stromal fibroblasts. No signs of testicular cancer were identified (Figure 5).

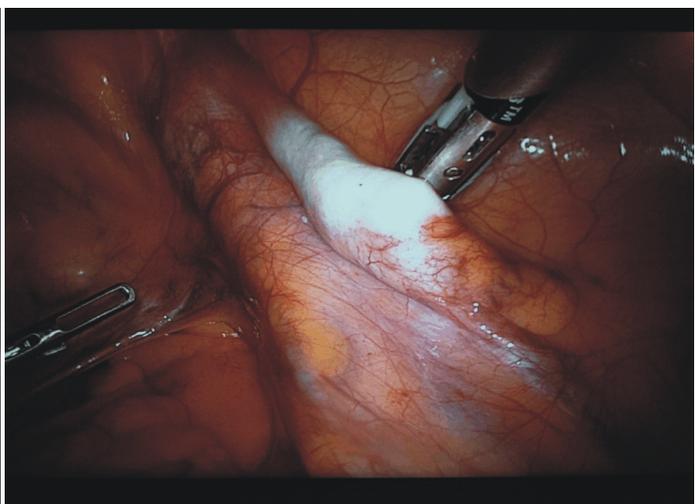
Mentally, the patient kept seeing herself as a woman, so the decision of telling her the truth was left to the parents. Therefore, no psychological counseling was yet needed.

**Figure 1 – Clinical aspect: female phenotype.**



**Figure 2 – Intra-abdominal testes: CT aspect.**

**Figure 3 – Intra-abdominal testes: laparoscopic aspect.**



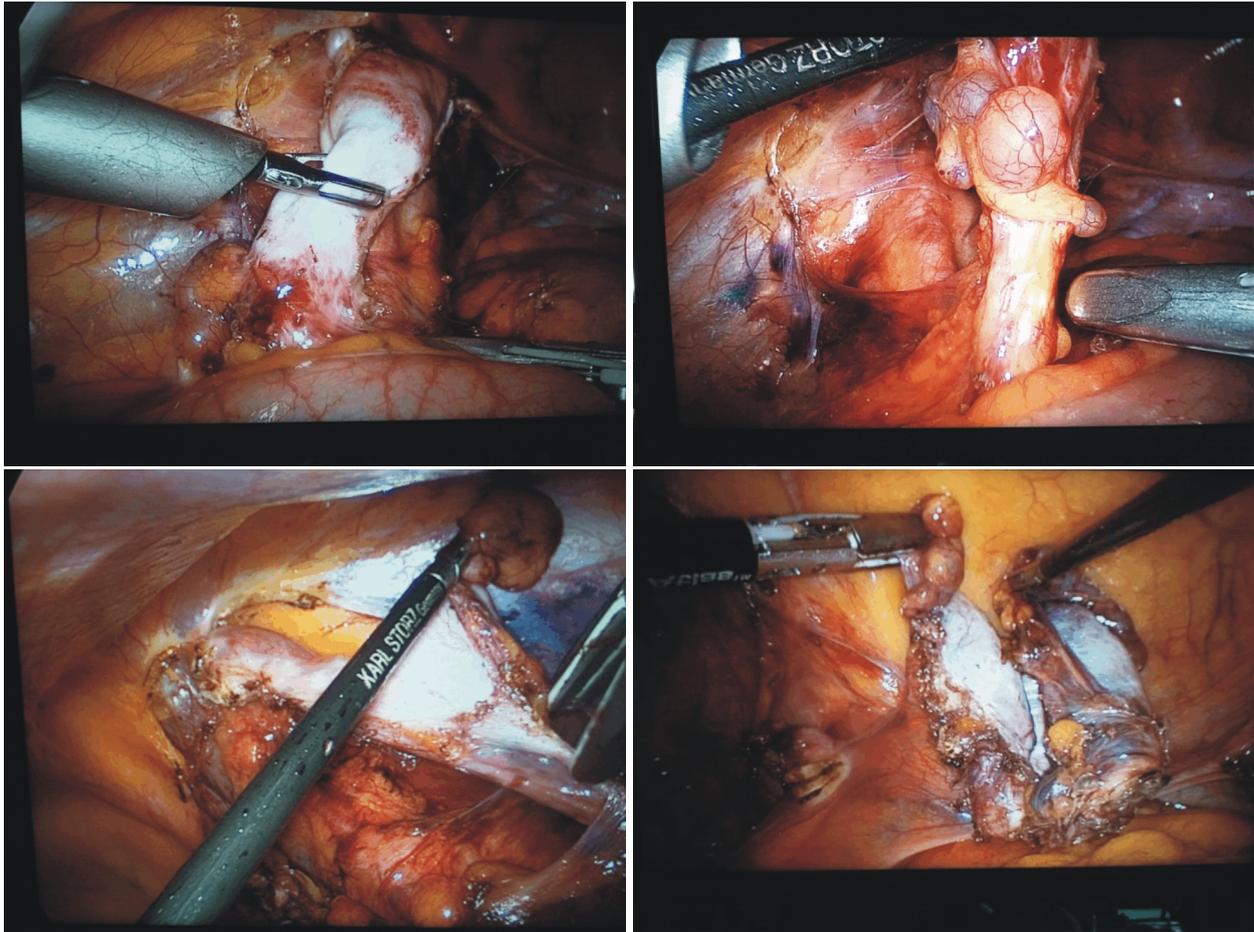


Figure 4 – Excision of the abdominal testes.

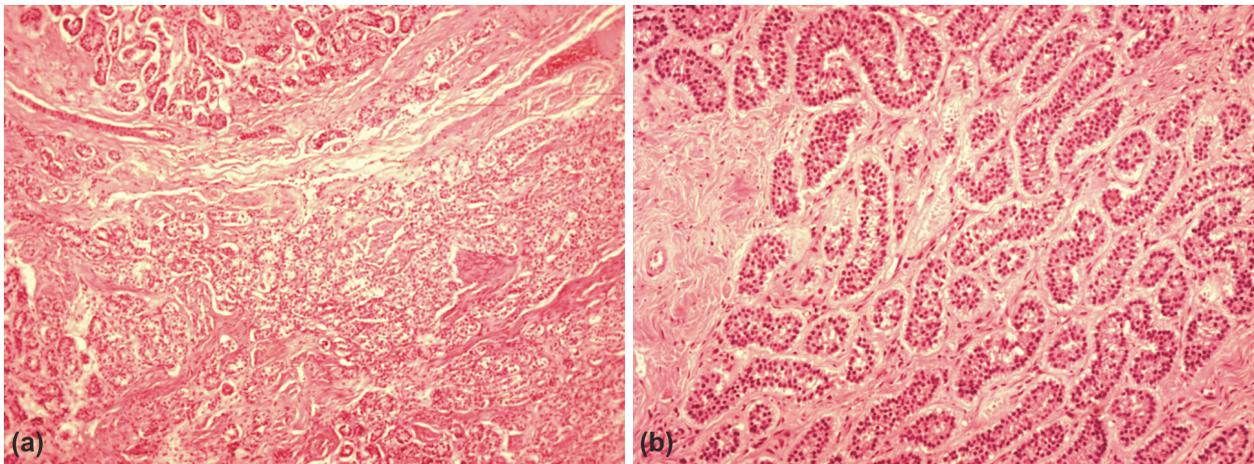


Figure 5 – Testes: atrophy of the seminiferous tubules. Histopathological aspect, HE staining: (a) ob. 10×; (b) ob. 20×.

### Discussion

The first problem with Complete Androgen Insensitivity Syndrome is the diagnosis. It requires many tests, some quite rare and frequently unavailable, so therefore it is often uncertain. Still, if everything can be performed, there are 5% of patients without an androgen receptor gene mutation, where the diagnosis is one of exclusion. Various other genetic abnormalities are ruled out through karyotype genetic mapping, and imaging techniques help settle the debate and point towards the necessary treatment, as was the case with our patient [13].

Then, there is the difficulty of assigning the gender,

but this is encountered mostly in Incomplete Androgen Insensitivity Syndrome, where there is a wild variety of sexual ambiguity. The factors that influence sex assignment are: the aspect of the genital organs and their postoperative functional capabilities, the surgical possibilities, the potential for virilization at puberty and for fertility and, very importantly, the projected gender identity. This can be estimated with the help of a psychologist. The decision has to be taken by the parents, only after all the variables are known. It usually happens at birth, so the genitoplasty is performed as soon as possible, though some physicians advise to wait until the child reaches the age of three.

Because around that age the gender identity begins to develop, and a correct assignment is more likely. Approximately 25% of patients are dissatisfied with the decided sex. Therefore, counseling is mandatory. In the case of Complete Androgen Insensitivity Syndrome, this situation is rare, the vast majority of patients seeing themselves as women [14].

Another topic at hand is the moment the orchiectomy should be performed, since the testes provide the natural levels of estrogens through the aromatizing of testosterone. Various studies show a risk of malignancy of undescended intra-abdominal testes of 3.6% at 25-year-old, and of 33% at 50-year-old. However, since hormone substitution therapy can be so easily administered nowadays, and artificial puberty is so similar to the natural puberty, there is no reason to wait and take an unnecessary chance. In our case, the patient had already gone through puberty, so the decision to operate was a lot less difficult [15].

In addition, the last issue is whether or not to disclose the entire pathology to the patient. The family should be informed, and together with the medical staff a resolution in this regard should be found. A psychologist should always be addressed before reaching a decision, so every aspect of this situation is known and understood. In our case, the patient was not made aware of the disease, in order to spare more confusion and pain, as the self-image was clearly of a heterosexual woman. The final decision rested with the family [16].

## ☐ Conclusions

Testicular feminization is a rare disease that must be diagnosed and treated through close work between gynecologists, endocrinologists, geneticists, urologists, anatomic pathologists and psychiatrists. Bilateral laparoscopic orchiectomy is a minimally invasive effective procedure of removing the intra-abdominal testes, in order to avoid their malignant transformation.

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