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Diagnosing and Managing Androgen Insensitivity Syndrome

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Abstract

Introduction: Androgen insensitivity syndrome is a rare congenital abnormality of genital organs revealing a female phenotype in a person with XY chromosomes. The aim of our work is to describe the clinical aspects, to determine the chromosomal sex and to report our therapeutic management. **Observation**: A 28-year-old woman with female phenotype, feminine voice, normal breast development, normal underarms and pubic hair, absence of menstruation, fusion of small and large vaginal lips leaving a small pertuis to serve as urethral meatus. On the dorsal surface of the large, left lip was a mass the size of a date. Hormonal balance was normal. A feminizing genitoplasty was performed as well as excision of the mass. Histological analysis of the mass concluded that it was a feminizing testicular. **Conclusion**: Androgen insensitivity syndrome is a rare abnormality of the genitals. Multidisciplinary management is essential both for the designation of the breeding sex and feminizing genitoplasty.

Keywords

Genital Malformation, Androgen, Genitoplasty, Vaginoplasty, Chromosomal Sex

1. Introduction

Androgen insensitivity syndrome, otherwise known as Morris syndrome or testicular feminization syndrome is a very rare disease characterized by an intersexual state in which there is presence of a female phenotype in an individual

with testicular, possessing an XY karyotype [1] [2] [3]. The birth of a child with an external genital organ abnormality is a social emergency that can present significant physical and psychological repercussions. The choice of the sex depends on the anatomy of the lesion, age of diagnosis, risk of gonadal degeneration and the maturity (especially pubertal) for the child. When all the anatomical and functional investigations have resulted in the choice of the definitive sex, a civil declaration can be made, and treatment put in place [4].

In 1940, Jost's work demonstrated that the removal of sexually undifferentiated gonads of a mammalian fetus leads to development of internal and external female organs.

The first publication on Androgen Insensitivity Syndrome (AIS) was done in 1953 by J. MORRIS [5], an American gynecologist. The case concerned a woman who had never seen her menses. Morphologically, she portrayed normal breasts development, external genitalia, pubic hair and a rare underarm, a short vagina and testicles.

Treatment must take into account the assigning sex which is usually female. It consists of: removal of the testicles (usually ectopic), effectuating a feminizing genitoplasty and psychological management of the patient and parents.

The aim of our work is to describe the diagnostic and therapeutic approach.

2. Patients and Method

OBSERVATION: DR, 28 years, 1.60 m, 57 Kg, repudiated twice successively by 2 spouses because of impossibility of penetration during coitus. She is taken to the urology consultation unit by a colleague (relative of the patient) who found her psychologically depressed. The interview visited the notion of primary amenorrhoea and allowed an appreciation of her voice (female type). Physical examination revealed a female phenotype, normal breast development, normal underarms and pubic hair, complete fusion of large and small lips (as if the perineum was abnormally elongated) leaving just a punctiform orifice serving as the urethral meatus. The catheterization of this meatus allowed an evacuation of urine from the bladder. Patient's informed consent was obtained for the chirurgical management and the using of photographies only for scientific aim. A mass, the size of a date and the form of an arch was visible and palpable at the level of the large left lip [**Figure 1**]. It was mobile under the skin. Endorectal ultrasound (vaginal ultrasound was impossible because of the absence of the vagina) the absence of a uterus and ovaries were noted. The pelvic tomodensitometry had also confirmed the absence of a uterus and ovaries. Hormonal balance reported an FSH rate of 0.80 mUI/ml (normal: 2 - 10), LH = 3.95 mUI/ml (normal: 2 - 9), Prolactin = 17.70 ng/ml (normal: 3 - 15) and testosterone = 1.74 ng/ml (normal: 3 - 8). Pre-operative assessment was also requested, especially: NFS, blood glucose, serum creatinine and blood grouping, the results were normal. After obtaining an informed consent from the patient and the parents, a feminizing genitoplasty was decided and executed. The surgery was performed

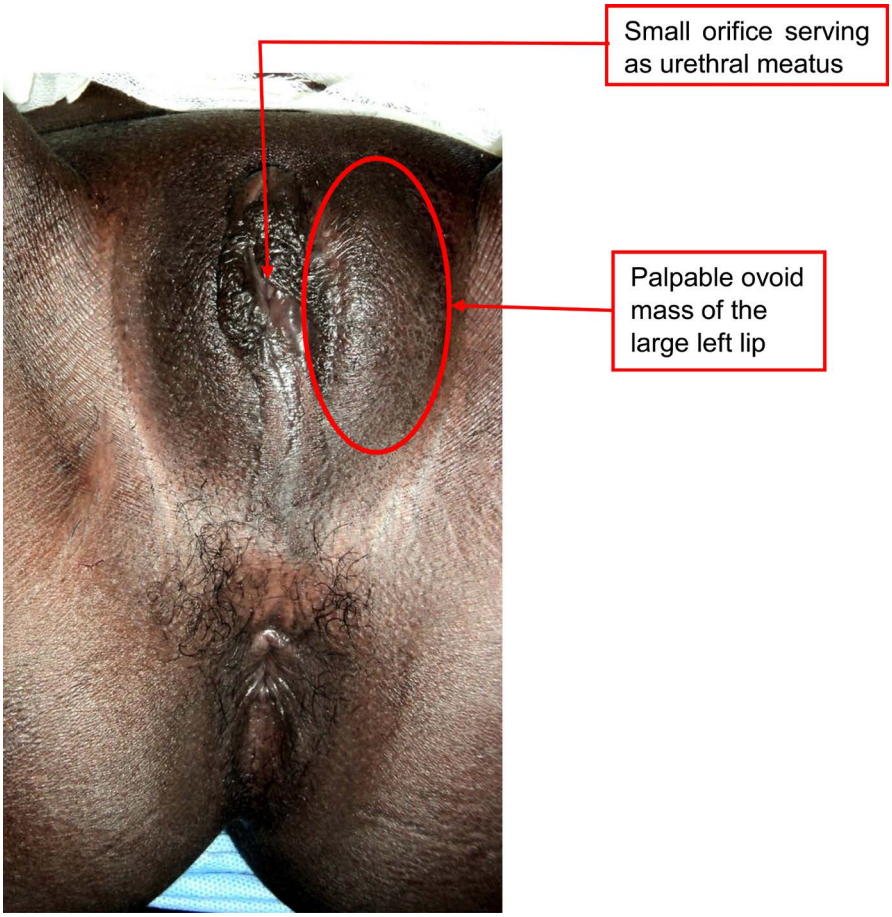


Figure 1. Coalescence of large and small lips.

under general anesthesia with oro-tracheal intubation in a patient who was gynecologically positioned. The urinary catheter was used as a guide. The first step was to perform a cautious vertical perineal incision 7 cm long to 1 cm below the meatus previously catheterized by a Foley Charrière 16 F probe in the direction of the perineum. Cautious dissection allowed the individualization of a short vaginal cavity 6 cm deep in the form of a cul-de-sac without a cervix (confirmed by the speculum examination in pre-operative) and a "vaginal urethral meatus" [**Figure 2**]. Each small lip was sutured by separate stitches with fine non-absorbable thread (3/0). A bold dressing separated the 2 labia minora. The second operative stage consisted of an incision straddling the mass of the left large lip, allowing us to individualize an ovoid formation resembling a testicle [**Figure 3**]. The operative sequences were simple. Multiple sessions of vaginal dilation did not result in sufficient vaginal depth (the normal vaginal depth was 8 cm). Moreover, the patient complained at each follow-up visit of her primary amenorrhea, which she did not accept despite the explanations for the absence of her uterus. Histological analysis of the surgical specimen concluded it as a feminizing testicle [**Figures 4(a)-(c)**]. At the end of the feminizing genitoplasty and in view of the verdict of the histology, a second informed consent was requested and obtained for the chromosomal sex determination which concluded: "presence of the SRY

locus results in favor of a male karyotype".

3. Comments = Discussion

Embryologic history

Any error in the choice of the breeding sex can have dramatic psychological

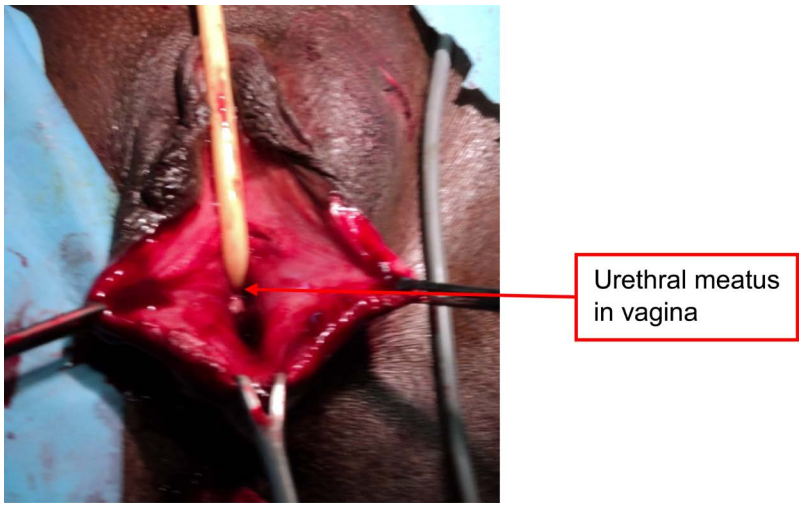


Figure 2. Urethral meatus in vagina.

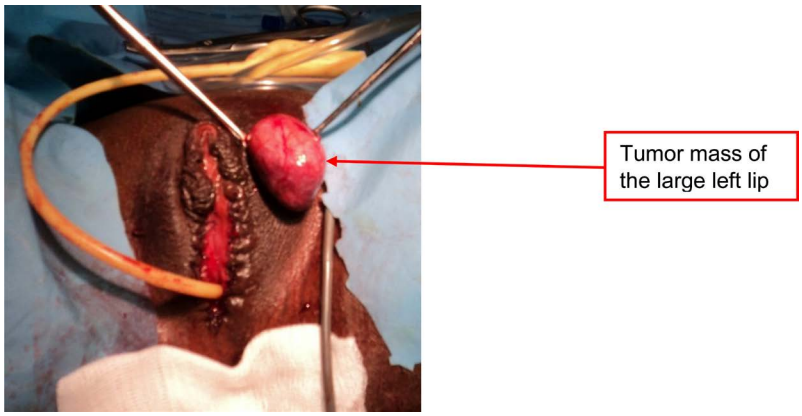
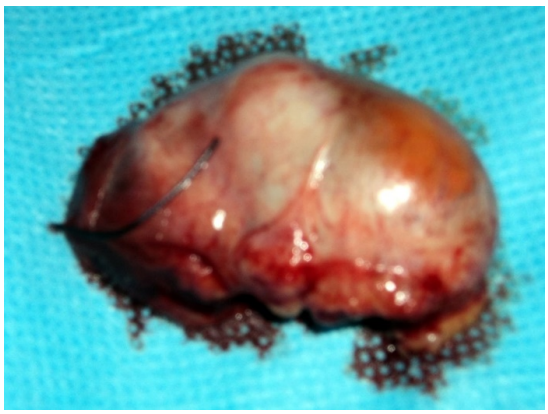
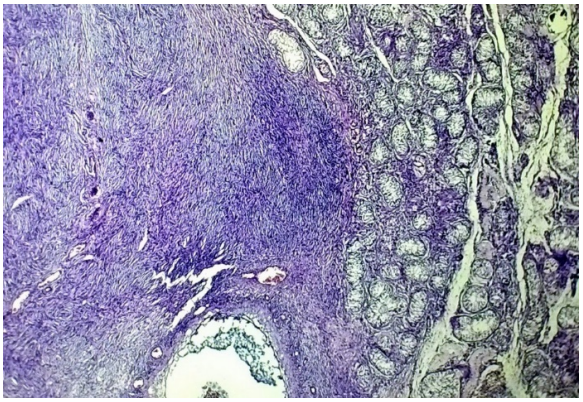


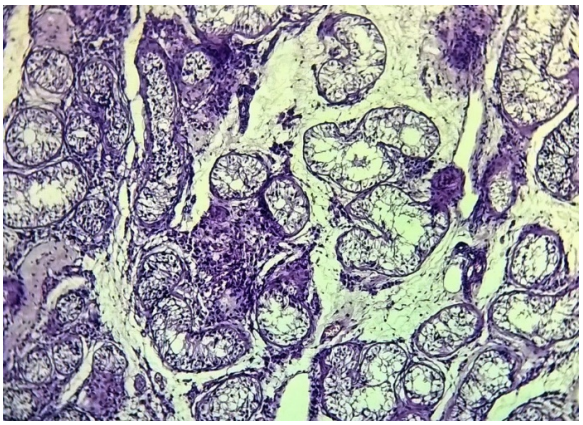
Figure 3. vaginoplasty.



(a)



(b)



(c)

Figure 4. (a) Macroscopic appearance of a testicle; (b) On the right, ovarian tissue. On the left, testicle (Hematoxylin and eosin staining, 400 X magnification); (c) Seminiferous tubules (Hematoxylin and eosin staining, 400 X magnification).

and social consequences for the patient and his/her family in the presence of sexual ambiguity. It should be pointed out that any suspicion of a pathology of sexual determination should be considered as an emergency and should lead, as soon as possible, to an etiology, subject to a vital risk (salt loss syndrome, adrenocortical hormonogenesis) and, to choose the breeding sex. Diagramatically, gonadal dysgenesis can be divided into three groups: pure, mixed and partial gonadal dysgenesis. The phenotype is polymorphic from complete feminization to the presence of a perineal or scrotal hypospadias. The gonads are located in the genital margins, in a more or less high position in the inguinal region or in the abdominal position. The presence or absence of Müller channels distinguished production or action abnormalities of testosterone from testicular dysgenesis in which the gonads secrete insufficient testosterone and anti-muller hormone [4]. Testicular organogenesis is under the control of a gene carried by the Y chromosome. The identification of this gene called TDF (Testis Determining Factor) encountered many difficulties. This region allowed the definition of a new possible locus for TDF. The SRY gene has recently been characterized in this small distal region of the Y chromosome. It is located on the short arm of

the Y chromosome, position Yp11.31 in men while commonly located in human beings, who present an XY system of sexual determination. The SRY gene induces differentiation of the gonad in the testis [6]. Androgens are synthesized in the Leydig cell and act within target tissues [7] [8]. The balance between androgens and estrogens is crucial in genital development. HCG (human chorionic gonadotrophin) produced by the placenta controls the growth of Leydig cells and stimulates fetal steroidogenesis until the pituitary gland/fetal gonad axis is established. Failure of one of the participants involved in this cascade may interfere with normal genital development.

Certain ubiquitous chemical, industrial, agricultural and horticultural pollutants present in our environment grouped under the name of "hormone switches" could present feminizing or demasculating effects in an unhealthy fetus. AMH (anti-Mullerian hormone) secreted by fetal servoli cells leads to regression of Mullerian structures (uterus, fallopian tubes and upper part of the vagina).

Clinical and therapeutic aspects

The safety and possibility of endorectal penetration (due to the absence of the vagina) of an ultrasound, seems to be the best imaging examination in search for Muilerian structures. Absence of the uterus, confirmed by endorectal ultrasound explained the absence of menstruation in the patient, despite her 28 years of life. Feminizing genitoplasty performed in the patient seemed to be the best option in accordance with her phenotype and her breeding sex, for she had lived for 28 years as a woman as evidenced by her "two marriages" divorces. Moreover, enormous difficulties are encountered in carrying out a masculinizing genitoplasty with often random results as regards aesthetic and functional aspects of the penis. Gonadectomy, practiced in our patient presented a four-fold objective. Aesthetics, due to the presence of the gonadal mass, is portrayed as disgraceful and the patient only wished that her spouse does not realize it. Diagnostic, where it was necessary to know the histological nature of the mass, whose origin was difficult to guess. Therapeutic, in order to avoid running the risk of cancer of an ectopic testicle. Cryptorchidism is seen as a well-known risk factor for testicular cancer. Indeed, the percentage of malignant transformation of dysgenetic gonads, in all categories, varies according to studies from 15% to 30% [7] [8] [9]. Moreover, the incidence of testicular cancer increased in France, where it was less than 1500 in 1990, reaching 2300 (InVS 2011 projection).The mortality linked to it, on the other hand, decreased from nearly 200 in 1990 to 86 in 2011 (InVS data). Psychological, because finally the woman felt she was female, with the possibility of having a spouse, enjoy sexual intercourse, a source of relief was also shared by the parents who lived this drama in pain and silence with their offspring. The Parents felt guilty about the state of malformation present in their offspring. If there is a clear consensus on gonadectomy, it must be recognized that the age at which it is to be practiced is controversial. Before puberty for some, after puberty for others. When gonadectomy is performed before puberty, estrogen replacement therapy is required to ensure normal breast development in accordance with the phenotype,

breeding sex and feminizing genitoplasty. After puberty, estrogen therapy is no longer justified because the androgens produced by the gonads are transformed into estrogens by aromatization and are sufficient to ensure normal breasts development. Short (shallow) vagina objectified in the patient is often reported by other authors [9]. Dilatations and intercourse often advised to improve the length (depth) of the vagina did not present expected results in our patient. Despite the depth of the vagina (6 cm), the patient reported satisfactory sexual intercourse. Another excellent alternative is vaginoplastic enlargement making use of sigmoid, presenting good results per promoter.

4. Conclusion

Androgen insensitivity syndrome is a rare congenital abnormality of the genitals revealing a female phenotype in a person with XY chromosomes. The diagnosis of androgen insensitivity syndrome is often late. Feminizing genitoplasty is in conformity with the breeding sex while gonadectomy avoids any risk of cancerization of the ectopic testicle.

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