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CASE REPORT

Androgen insensitivity revealed by surgery in elderly identical twins

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Abstract Two elderly identical twin sisters with inguinal hernias and malignant gonadic tumors were diagnosed during surgery as having complete androgen insensitivity syndrome. Androgen insensitivity syndrome, also referred to as testicular feminization, is an X-chromosome-linked genetic condition in which the tissues of a genotypic male are unresponsive to androgens because of an anomaly of the androgen receptor. This results in feminization of the external genitalia. The internal genital organs including the cranial part of the vagina, cervix, uterus, and fallopian tubes are absent because of testicular inhibition during embryonic development. Patients most frequently present as young females with asymptomatic bilateral inguinal hernias. They may undergo normal puberty but have primary amenorrhea. Rarely, the diagnosis may follow a workup for infertility. As in cryptorchidia, the testicles are prone to malignant transformation and require that orchidectomy be performed, usually after puberty.

Keywords Male pseudohermaphrodism · Androgen insensitivity · Infertility · Gonadic tumors · Inguinal hernia · Amenorrhea

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Patients

A 77-year-old nulliparous woman experienced left iliac fossa pain. Palpation revealed a mobile mass in the left fossa. The patient's physical appearance was that of a normal female with developed breasts and normal external genitals but scarce pubic and axillary hair. The patient's medical history included right hemiparalysis, pudendal nerve neuralgia, and left inguinal hernia repair 4 years previously. Computerized tomography confirmed the presence of a round 5-cm soft tissue mass (Fig. 1). At positron emission tomography, there was intense radionuclide uptake by the lesion. Laparoscopy revealed an enlarged left gonad but no peritoneal tumor implants. Early-stage ovarian cancer was suspected, and bilateral ovariectomy was performed. No uterus was found, but remnants of Fallopian tubes were seen, and it was assumed that the patient had undergone hysterectomy during previous surgery. Pathological analysis diagnosed a rare well-differentiated Sertoli–Leydig cell tumor of the ovary. Postoperatively, we were intrigued by the fact that the patient had a twin sister who closely resembled her. When asked, the patient's sister confirmed that neither she nor her twin sister had ever had menstruations. When examined, the patient's sister presented a mass in her right iliac fossa and an ipsilateral inguinal hernia containing a nonreducible elastic mass. Computerized tomography showed a 10-cm bilobar tumor extending into the inguinal canal (Fig. 2). At laparoscopy, we found a right adnexal tumor partially engaged in the inguinal canal. Cranially from it arose a vascular pedicle and another cord-like structure coursed in the direction of the obturator ring. Bilateral ovariectomy was performed. As with her sister, no uterus was found, and pathology showed an 11-cm Sertoli–Leydig cell tumor. Immunofluorescence studies with antibodies directed

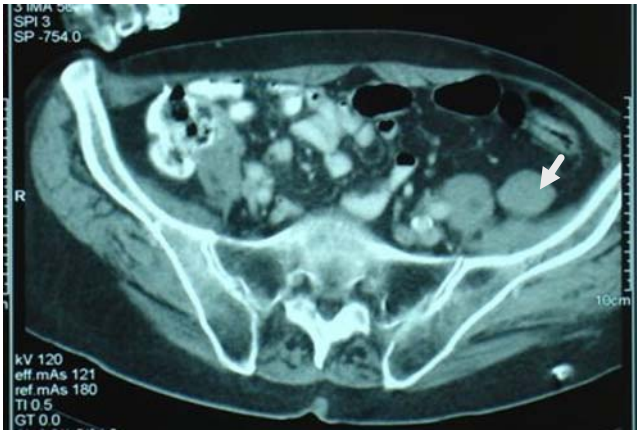

Fig. 1 Patient 1: computerized tomography showing a 5-cm soft tissue mass in the left iliac fossa (*arrow*)

against the Y chromosome on buccal cavity smears showed that both sisters had a 46XY genotype. Fluorescent in situ hybridization studies on blood lymphocytes showed no anomalies in the sex-determining region gene on the Y chromosome (SRY), corroborating the diagnosis of complete androgen insensitivity syndrome. Polymerase chain reaction amplification and sequencing of the eight exons of the androgen receptor (AR) gene showed that both sisters carried the p.Glu353X (c.1057G>T) mutation in exon 1 of the AR gene.

Discussion

Androgens and target-organ androgen receptors play a crucial role in male differentiation of the XY embryo [1] (Fig. 3). Before 6 weeks of gestation, all embryos possess both Mullerian and Wolffian ducts and undifferentiated external genitals. By default, the primordial gonad develops into an ovary. In XY embryos, the testes-determining factor causes differentiation of the gonad into a testis. Testes-determining factor is a DNA-binding protein transcription factor encoded by a gene on the short arm of the Y chromosome, known as the sex-determining region of the Y chromosome [2]. Testicular differentiation is, therefore, not androgen-dependent. Between 6 and 8 weeks of gestation, Sertoli cells within the testis secrete an anti-Mullerian hormone which causes regression of the female internal genitalia known as Mullerian ducts (Fallopian tubes, uterus, cervix, and proximal part of the vagina) [3]. During the following 4 weeks of gestation, testosterone secretion by the testis induces differentiation of the Wolffian ducts into epididymides, vasa deferentia, and seminal vesicles [4]. Development of the prostate, prostatic urethra, and male external genital organs (penis, urethra, and scrotum) appears to be the result of androgenic stimulation by dehydrotestosterone, the more potent metabolite of testosterone [4]. To achieve this, testosterone is transformed by an enzyme (5-α reductase 2) normally present in target organs. At puberty, androgen secretion and target-organ androgen receptors are also necessary to achieve complete masculinization. Pubic and axillary hairs, beard, acne, adult perspiration odors, and low voice tone are all manifestations of androgen impregnation during puberty.

Androgen insensitivity syndrome (AIS) also known as Morris syndrome or testicular feminization syndrome is the most common cause of male pseudohermaphrodism, affecting 1/20,000 male births [5]. It is a genetic X-chromosome-linked recessive disorder but can occasionally occur sporadically through de novo mutations. The genetic defect involves a segment of the long arm of the X chromosome that codes for the androgen receptor. Over 200 different mutations have been ascribed to AIS which explains the phenotypic polymorphism [1]. Androgen receptor defects form a continuum, and the resulting impact on androgen receptor function will determine the degree of feminization. It is common to distinguish between complete and partial androgen insensitivity, and the two forms are usually not found within a same pedigree [6]. However, different phenotypes of partial AIS may be present within a single family. A grading system for AIS is based on the degree of feminization of the external genital organs at birth [7] (Fig. 4). Grade 1 patients have the mildest form of androgen insensitivity. Their external genital organs are masculine. This group comprises, phenotypically, normal men with infertility due to oligo/azoospermia and those with reduced virilization at puberty. Also in this group are patients with a rare form of X-linked motor neuron disease (Kennedy syndrome) in which signs of androgen resistance appear only after the third decade of life [8]. Prior to developing neurological symptoms, the patients often present gynecomastia,

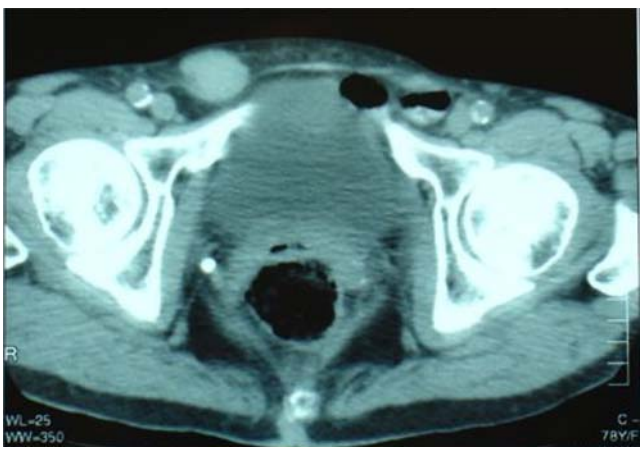

Fig. 2 Patient 2: computerized tomography showing a soft tissue mass engaged in the right inguinal canal

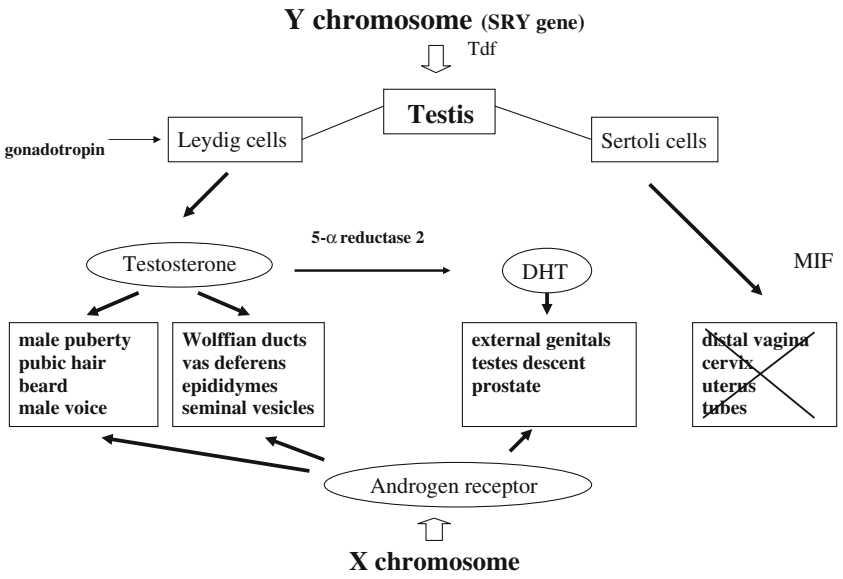

Fig. 3 Physiology of sexual differentiation. *SRY* Sex-determining region of Y chromosome, *Tdf* testis-determining factor, *MIF* Mullerian-inhibiting factor, *DHT* dehydrotestosterone

azoospermia, impotence, and testicular atrophy. Grade 3 patients exhibit the most significant genital ambiguity.

At the other end of the spectrum, grade 7 patients are those with complete androgen insensitivity. At birth, their external genital organs are unequivocally female. Their internal genital organs are lacking because of physiological inhibition by Mullerian-inhibiting factor secreted in utero by the testes. Remnants of Wolffian structures, such as vestigial vas deferens or epididymis, may sometimes be found but, usually, internal genital organs are limited to the presence of two undescended or partially descended testes. Pubic and axillary hairs are scant or absent at puberty. Pubertal breast development ranging from mild gynecomastia to large breasts can occur with all grades of AIS and tends to be more pronounced with increasing androgen insensitivity. This is due to the loss of feedback resulting in increased pituitary secretion of luteinizing hormone with overstimulation of Leydig cell production of testosterone and estradiol. Testosterone also undergoes aromatization to estradiol in peripheral tissues. Complete androgen insensitivity results in an unequivocally feminine appearance at adult age.

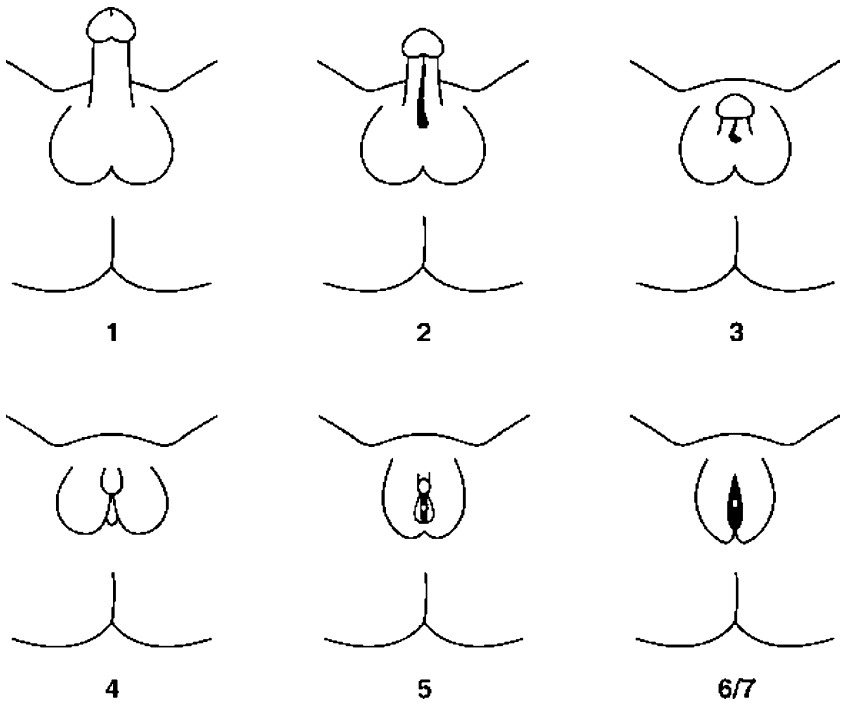

Fig. 4 Grading system according to the degree of feminization of external genitalia

As in cryptorchidia, the testes of patients with androgen insensitivity are prone to malignant transformation. The risk of developing a malignant germ cell tumor (seminoma) rises from 3% at age 20 to 30% at age 50 [9]. Low-grade nongerm cell (Sertoli and Leydig cells) tumors can also develop as well as mixed tumors (hamartomas) containing germ cell, Leydig cell, and Sertoli cell elements. The overall incidence of gonadal neoplasia remains difficult to evaluate, but it is thought that neoplasia very seldom develops before puberty. The overall risk of malignancy is estimated to be 6–9% [10]. Benign tumors develop in 25% of patients. Prevention of testicular cancer mandates orchidectomy in patients with AIS. This can be performed in early childhood or be delayed till after puberty, but usually before age 20.

A frequent mode of presentation of AIS is that of a young woman with normal puberty but with no menstruations and scant/absent pubic and axillary hairs. Up to 1–2% of young girls with asymptomatic bilateral inguinal hernias are thought to have complete androgen insensitivity syndrome [11]. It has been suggested that during bilateral hernia repair in a young girl with herniated gonads, the surgeon should verify the presence of normal Mullerian structures (fimbriae and tubes) by pulling the gonads outwards. Their absence is highly suggestive of the diagnosis. If androgen insensitivity syndrome is suspected, a frozen section biopsy of the gonad should be performed. Evidence of normal testicular tissue at pathology will corroborate the diagnosis. The hernias should be repaired, and the gonads placed subcutaneously below the skin incision to facilitate later orchidectomy. Gonadectomy is not indicated during hernia repair when the diagnosis is first suspected. This decision will be left until later when the patient and her family have been adequately counseled and have given their informed consent [12]. Gynecological evaluation will confirm the absence of a uterus and cervix. Genetic studies will reveal an XY genotype.

Sex assignment can be a significant dilemma facing these patients, their parents, and healthcare professionals. Female assignment remains the most frequently chosen option, but male assignment has gained popularity during the past decade. While assignment of female sex to patients with complete AIS and male sex to those with mild forms of AIS may appear self-evident, the decision becomes very difficult in patients with highly ambiguous external genital organs. This is compounded by the fact that the degree of masculinization and penile growth at puberty is, to a large extent, unpredictable. If male assignment is chosen, the infant will need to undergo repair of hypospadias, closure of midline pouch, and placement of testes in the scrotum if possible. High-dose testosterone can sometimes achieve virilization at puberty. Gynecomastia can be corrected, and the gonads can be removed sometime after puberty to prevent the risk of cancer. If female assignment is chosen, gonadectomy in childhood is performed to halt masculinization and to prevent testicular neoplasia. When necessary, the vaginal opening is enlarged, and the clitoris is reduced. Estrogen is administered at puberty. Vaginal bougienage or surgery may be necessary to lengthen the vagina. In complete AIS, gonadectomy is best postponed till after puberty as the testes also produce estrogens that encourage breast development and female body shape at puberty. More recently, it has been suggested that surgery be delayed until adolescence when the patient is capable of choosing his/her sex. It would seem, however, that to achieve successful gender identification, the decision to rear the child as a girl or a boy should be made as soon as possible after birth. Also, it may be very troubling for a child to discover he is morphologically different from other children.

Androgen insensitivity syndrome also poses a difficult ethical issue. Should the diagnosis be revealed to the patient or should it be concealed on the assumption that it will cause permanent emotional distress to the patient? With the advent of modern information technology, it is likely that a young woman who wants to find out why she is not menstruated or has no pubic/axillary hair will get cued as to her condition simply by browsing on the internet. Nor will she content herself with a vague diagnosis of "idiopathic infertility" given by a healthcare professional. Being told the truth in a frank and sensitive way is probably preferable [13].

Conflict of interest There is no actual or potential conflict of interest in relation to this article.

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