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Complete androgen insensitivity syndrome: a case report and literature review

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Abstract

Complete androgen insensitivity syndrome (CAIS) is a rare disease that can be easily misdiagnosed. Before puberty, this condition is easily misdiagnosed as an inguinal hernia. This case report describes a 31-year-old phenotypically female patient with CAIS who was misdiagnosed twice previously with an inguinal hernia. Her karyotype analysis showed that she was 46, XY. She underwent a bilateral gonadectomy and long-term hormone replacement therapy. A Leydig cell tumour of the right testis was diagnosed postoperatively. This report also reviews the current understanding of the diagnosis and treatment of CAIS.

Keywords

Complete androgen insensitivity syndrome, gonads, hormone replacement therapy, case report

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Introduction

Complete androgen insensitivity syndrome (CAIS) is one of the disorders of sexual development. The Office of Rare Diseases of the National Institutes of Health classifies CAIS as a 'rare disease'.[1] Patients with CAIS are characterized by having a chromosome karyotype of 46, XY and their gonads are testicles; but their bodies are completely insensitive to androgen, resulting in the appearance of a completely female phenotype.[2] After birth, the child is often raised as a female baby. Before puberty, this condition is easily misdiagnosed as an inguinal hernia.[2] This case report describes a female patient that had been misdiagnosed as having an inguinal hernia twice.

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Case report

In November 2021, a 31-year-old patient who presented phenotypically as a female and lived as a female presented to the Department of Gynaecology, SSL Central Hospital of Dongguan City, Dongguan, Guangdong Province, China. In terms of her medical history, she had been born with the appearance of a female baby. At approximately the age of 1 year, she had been operated on because of an inguinal hernia. The operation had been stopped because of 'massive haemorrhage' during the procedure. At the age of 14 years, she was operated on again because of an inguinal hernia. The specific details of the surgical procedure remain unknown. At the age of 16 years, she was examined and found to have no uterus or ovaries that caused 'primary amenorrhea'. Her karyotype analysis showed that she was 46, XY. She has one younger brother and one younger sister. Both of her siblings have shown normal physical development. The younger sister has regular menstruation and has had an induced abortion.

A physical examination at the current presentation showed the following: height 166 cm and weight 55 kg. She had good nutrition, no swelling of the lymph nodes on the body surface, no laryngeal nodes on the neck, no axillary hair, full mammary glands on both sides, small areola, nipple dysplasia and the nipples were depressed. There was no chest hair, full bilateral groins and an old surgical incision approximately 6 cm long could be seen on both groins. Gynaecological examination showed the following: female vulva, no perineal hair, the vagina was unobstructed, the top of the vagina had a blind end and the total length of the vagina was approximately 6 cm.

An auxiliary examination at the current presentation showed the following results for the sex hormone tests: oestradiol (E2) 63.8 pg/ml, testosterone (T) 5.34 ng/ml, progesterone (P) 0.267 ng/ml, luteinising hormone (LH) 29.3 mIU/ml, follicle stimulating hormone (FSH) 16.1 mIU/ml and prolactin (PRL) 252 IU/ml. Pelvic magnetic resonance imaging showed the following: no uterus or bilateral ovaries were found; abnormal signal shadows on the bilateral groins (51 mm × 27 mm on the right and 46 mm × 21 mm on the left), which were considered as cryptorchidism.

The patient was clinically diagnosed as having complete androgen insensitivity syndrome and bilateral cryptorchidism. Because the patient's chromosome karyotype was 46, XY, Mayer-Rokitansky-Küster-Hauser syndrome could be excluded. The breasts of the patient were fully developed and the vulva was completely female, so it was possible to exclude 5 α-reductase type 2 deficiency.

In terms of treatment, at our suggestion, the patient underwent abdominal bilateral inguinal testicle resection in the Department of Urology, SSL Central Hospital of Dongguan City, Dongguan, Guangdong Province, China. During the operation, bilateral testicles were found under the external oblique muscle on both sides, both of which were hard. The postoperative pathological findings were as follows: (i) left inguinal mass that was consistent with cryptorchidism; (ii) right inguinal mass that based on histological and immunohistochemical results was consistent with a testicular stromal cell tumour. The immunohistochemistry results for the right inguinal mass showed the following: cluster of differentiation (CD)117 (–); lymphatic endothelial marker monoclonal antibody (–); ki67 1% (+); cytokeratin (CK) (+); epithelial membrane antigen (–); CD30 (–) ; glypican 3 (–); CK19 (–); calretinin (+); CD99 (+); melanoma antigen (+); vimentin (+); α-inhibin (+) (Figures 1–3). A supplementary diagnosis was that of a Leydig cell tumour of the right testis. It was a benign testicular tumour.

Sex hormone tests were undertaken again 14 days after the operation and showed the following: E2 5.0 pg/ml, T 0.152 ng/ml, P 0.05 ng/ml, LH 75.8 mIU/

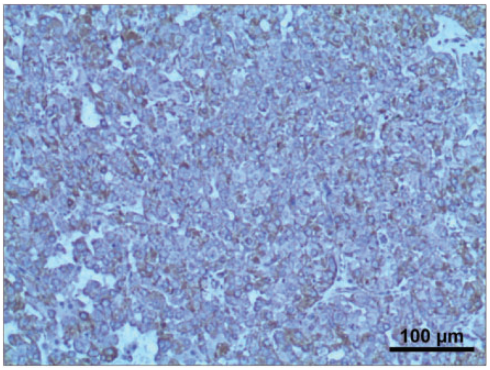

Figure 1. Representative photomicrograph showing the positive immunohistochemical staining for α-inhibin of a specimen from a right inguinal mass removed from a 31-year-old female with complete androgen insensitivity syndrome (scale bar 100 μm). The findings were suggestive of a testicular stromal cell tumour. The colour version of this figure is available at: http://imr.sagepub.com.

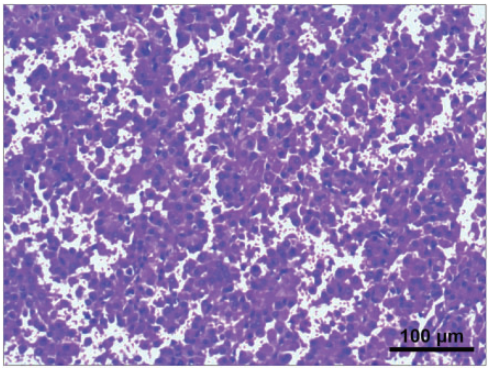

Figure 2. Representative photomicrograph of a specimen from a right inguinal mass removed from a 31-year-old female with complete androgen insensitivity syndrome showed the following: the tumour cells were round and grew diffusely; the cytoplasm was strongly eosinophilic; and the nuclei were round with little atypia (haematoxylin and eosin, scale bar 100 μm). The colour version of this figure is available at: http://imr.sagepub.com.

ml, FSH 114 mIU/ml and PRL 207 IU/ml. The patient was administered the following postoperative treatment: 2 mg oestradiol valerate tablets orally once daily. After

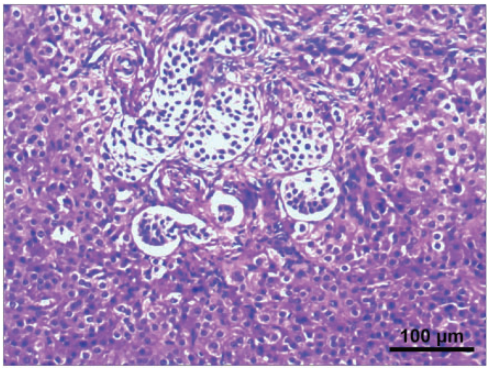

Figure 3. Representative photomicrograph of a specimen from a right inguinal mass removed from a 31-year-old female with complete androgen insensitivity syndrome showed the following: spermatogenic cells were stunted and the Sertoli cells were immature in the seminiferous tubules (haematoxylin and eosin, scale bar 100 μm). The colour version of this figure is available at: http://imr.sagepub.com.

receiving this medication, her E2 level increased to 48.4 pg/ml. Since the operation, she has not felt unwell and has been reviewed regularly. A lifetime of follow-up has been suggested to the patient in addition to undertaking genetic tests and family investigations. Written informed consent for publication of this case report was obtained from the patient. The reporting of this study conforms to the CARE guidelines.[3]

Discussion

This current case report describes the typical diagnosis and medical treatment process that is followed in a representative patient with CAIS. The pathogenesis of CAIS is caused by the mutation of the androgen receptor (*AR*) gene located on the Xq11–12 region.[4] According to the literature, hundreds of genetic mutations of the *AR* gene have been confirmed, most of which originate from the germline of the patient's mother; but the *AR* mutation of some patients originates from a new mutation

of the *AR* gene that arises during the post-zygotic phase.[5] A retrospective analysis of 64 patients with androgen insensitivity syndrome showed that the patients with mutations in the ligand-binding domain (LBD) of the *AR* gene had more significant androgen resistance and lower scores for masculinity, which suggests that LBD mutations are more likely to lead to CAIS.[6] Unfortunately, the current patient has not yet undergone a full genetic examination and a complete family survey. These examinations will be undertaken as part of her ongoing follow-up.

The endocrine characteristics of patients with CAIS show normal or slightly increased testosterone levels in men, a normal FSH level and normal or slightly increased LH levels due to the negative feedback of the hypothalamic-pituitary system. The following is a summary of the typical clinical features of patients with CAIS: (i) the final height of a CAIS patient is approximately 165.7 ± 8.9 cm, which is higher than the average height for females, but lower than the average height for males. This is because the bone system of CAIS patients does not respond to androgens, resulting in the height of patients being unable to reach the level of normal adult males; but it is affected by the growth control gene on the Y chromosome, so CAIS patients are generally taller than unaffected females;[7] (ii) in terms of mammogenesis, at puberty, excessive androgens in the blood are aromatized to produce oestrogen, so the breasts of the typical CAIS patient are generally well developed. Because nipple development depends on androgens, these patients often show poor nipple development; (iii) there is typically less axillary hair and perineal hair (rare or absent) due to androgen resistance; (iv) there is an absence of female internal genitalia due to the secretion of anti-Mullerian hormone by the testes, which inhibits the formation of the fallopian tubes, uterus and upper part of the vagina. The lower third of the vagina develops from the urogenital ridge. Therefore, the patient has a short and shallow vagina with a blind end at the top. The vaginal length of such patients is generally 2.5–8.0 cm;[2] (v) in terms of cryptorchidism, a British study showed that nearly 57% of patients with CAIS have inguinal hernia, and some patients were diagnosed as 'hernia' in infancy or childhood.[8] The incidence rate of inguinal hernia in children is approximately 1–4%.[2] The incidence of inguinal hernia in male children is 10-times that in female children.[2] For female children with an inguinal hernia, physicians should consider CAIS and undertake a karyotype analysis.[8]

A literature review of the controversial points in terms of the treatment of CAIS patients was undertaken. In terms of whether and when to remove the gonads, the probability of gonadal tumours in patients with CAIS is higher than that of normal men. For example, studies showed that the occurrence of gonadal tumours in patients with CAIS is related to age.[9,10] A previous study reported that the risk of testicular germ cell tumours in patients with CAIS increased with age; in prepubertal patients with CAIS it was 0.8–2%, and estimated to be 3.6% at 25 years of age and 33% at 50 years of age.[11] A systematic review showed that among 456 patients with CAIS who underwent gonadectomy or gonadal biopsy, 6.14% had precancerous lesions, most (82.14%) of them occurred after 12 years of age, 1.3% of them were malignant lesions and all of them were in adult women.[12] Therefore, taking into account the lower rate of gonadal malignancy during and before puberty and the benefits of gonadal preservation, most experts recommend gonadectomy as early as possible after puberty.[13] However, some patients are worried about the risk of surgery and are unwilling to accept long-term hormone replacement therapy after the procedure. An analysis of 98 adult patients with CAIS (aged > 20 years) from four

articles identified by a retrospective literature review, found that 14 patients had pathologically confirmed malignant testicular tumours.[14] The review estimated a risk of gonadal malignancy of 14% (range, 0–22%) in adults with CAIS.[14] A retrospective observational study analysed 30 patients with CAIS aged 16–34 years (mean age, 22.3 years) and found that nine patients had gonadoblastomas, giving a malignancy rate of 30%.[15] The most difficult problem in maintaining gonads is how to identify malignant gonads or carcinoma *in situ* early. Some scholars have proposed a screening plan, including regular imaging of the testes and serological examinations, ultrasonography or nuclear magnetic resonance examinations, alpha-fetoprotein, beta human chorionic gonadotropin, lactate dehydrogenase, optional placental alkaline phosphatase, LH, FSH, testosterone and inhibin B, but these are not specific detection methods for gonadal malignant transformation in CAIS patients.[16] Some scholars believe that the development of specific microRNA detection will be an accurate and sensitive method for the early identification of gonadal tumours, such as mir-371-3, but this has not been clinically confirmed.[17] In addition, some specific single nucleotide polymorphisms have been found to be helpful in the prediction of testicular germ cell tumours in patients with CAIS.[18] Whether to retain the gonads in patients with CAIS remains controversial. For patients who strongly desire to keep their gonads, the physician should fully inform them of the risks and provide ongoing follow-up. If they experience a dull pain or discomfort, or there is a change in the imaging examination, a gonad biopsy or resection should be performed.

Hormone replacement therapy (HRT) is essential for patients with CAIS who have had their gonads removed. For patients with gonadectomy before adulthood, HRT should ensure that breast and height development reach the level of their peers. At the same time, attention should be paid to the patient's bone mineral density, bone and muscle development, as well as social psychological and sexual psychological maturity, which requires the assistance of paediatricians. For adult CAIS patients with gonadectomy, the purpose of HRT is to maintain the female secondary sexual characteristics, prevent bone loss, ensure cardiovascular health and mental health. HRT should be continued until the average natural menopause of unaffected women. At present, percutaneous oestradiol preparation is recommended.[19,20] Some scholars advocate the use of testosterone as the HRT scheme for CAIS patients.[21] A multicentre, randomized, double-blind trial compared percutaneous oestrogen (1.5 mg/day) and percutaneous testosterone (50 mg/day).[21] The study demonstrated that testosterone was as well tolerated and as safe as oestrogen; and compared with oestrogen, testosterone treatment was more helpful in improving sexual desire, so it is more suitable for CAIS patients with decreased sexual desire.[21] However, transdermal oestradiol or testosterone treatment led to elevated blood lipids in patients with CAIS.[22]

Patients with CAIS often have a short blind-ended vagina, so the need for vaginoplasty should be considered. Some CAIS patients can have a satisfactory sexual life without medical intervention. For patients with difficulties in their sexual life, a vaginal mold can be used to press inward at the position of the navicular fossa mucosa in the vestibule of the vulva and vagina.[23] After approximately 5 months of vaginal dilator therapy, a longer vagina can be achieved.[24] This method is used as the first-line treatment. For patients who are not satisfied with the effect of the mold pressing method or have extremely short vaginas, vaginoplasty should be adopted.[23] At present, there are many such operations and each procedure has its own advantages and disadvantages. There is no consensus

about which is the best option. The operation should be completed in a centre with considerable experience in the diagnosis and treatment of CAIS.[24]

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Author contributions

Min Guo performed the clinical diagnosis and treatment, and wrote the manuscript. Cui-Fen Li and Yan-Yan Liu provided guidance for the diagnosis and treatment. Jin-Cheng Huang provided help in writing the manuscript.

Declaration of conflicting interests

The authors declare that there are no conflicts of interest.

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