

Rare Case of Complete Androgen Insensitivity Syndrome

Review began 02/06/2024
Review ended 02/16/2024
Published 02/20/2024

© Copyright 2024

Fava Spessoto et al. This is an open access article distributed under the terms of the Creative Commons Attribution License CC-BY 4.0., which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Luís Cesar Fava Spessoto¹, Júlia Saraiva Avelino Silveira¹, Andres Menacho Abularach¹, Gustavo Santana Garcia¹, Matheus Castro Almeida¹, Guilherme Cerqueira Gonzales¹, Ana Clara Nagle Spessoto², Fernando Nestor Facio Jr.¹, Mateus Henrique Silva Faria¹

1. Urology, Faculty of Medicine of São José do Rio Preto, São José do Rio Preto, BRA 2. Medicine, Medical School of Catanduva, Catanduva, BRA

Corresponding author: Mateus Henrique Silva Faria, mateus.h.mx@hotmail.com

Abstract

Androgen insensitivity syndrome is a rare X-linked recessive condition in which patients present a female phenotype. After complete androgen insensitivity syndrome (CAIS) diagnosis, the timing of gonadectomy should be evaluated, considering the risks and benefits of this procedure. This paper reports an uncommon case of complete androgen insensitivity syndrome diagnosed belatedly in an adult patient. Surgical treatment was deemed necessary due to the elevated risk of gonadal malignancy.

Categories: Genetics, Urology

Keywords: treatment, urology, androgen receptor, male pseudohermaphroditism, androgen insensitivity

Introduction

Androgen insensitivity syndrome (AIS) is a rare genetic condition linked to the X chromosome, in which individuals with 46,XY karyotype have a complete (CAIS) or partial (PAIS) impairment of pre- and postnatal virilization and develop a female phenotype [1].

The mutation occurs in the androgen receptor gene, and despite having normal testosterone synthesis, the individual does not develop male characteristics. However, as they have a normal estrogen receptor, the development of female sexual characteristics takes place [2].

Clinical suspicion typically arises during puberty in patients with a female phenotype and primary amenorrhea, reduced pubic and axillary hair, persistent childlike voice, and dyspareunia. Less frequently, it occurs before puberty in cases where patients present with bilateral inguinal hernia, a short vagina, and elevated levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone [3].

Individuals with CAIS present excellent feminization at puberty (normal or augmented breasts, acne-free and body contour) that occurs in response to estrogen produced by testicular and peripheral aromatization of testosterone [4].

In this report, we describe an uncommon case of complete androgen insensitivity syndrome diagnosed belatedly in an adult patient.

Case Presentation

A 33-year-old female patient was referred to the urology outpatient clinic for evaluation due to elevated levels of total testosterone (674 ng/dL) and elongated nodular images adjacent to the ovaries observed in a previous pelvic magnetic resonance imaging (MRI). Additionally, the medical record indicated a karyotype of 46 XY with a provisional diagnosis of Morris syndrome.

Abdominal MRI revealed oval-shaped, well-defined solid images adjacent to the bilateral iliac vessels, measuring 2.2 x 1.7 cm on the right and 2.4 x 1.0 cm on the left, potentially corresponding to male gonads (Figure 1). Adjacent to these images, thin-walled and regular cystic formations are observed, with the largest measuring 1.7 x 1.6 cm on the right, suggesting an association with Müllerian duct cysts located in the pelvic cavity.

How to cite this article

Fava Spessoto L, Avelino Silveira J, Abularach A, et al. (February 20, 2024) Rare Case of Complete Androgen Insensitivity Syndrome. Cureus 16(2): e54550. DOI 10.7759/cureus.54550

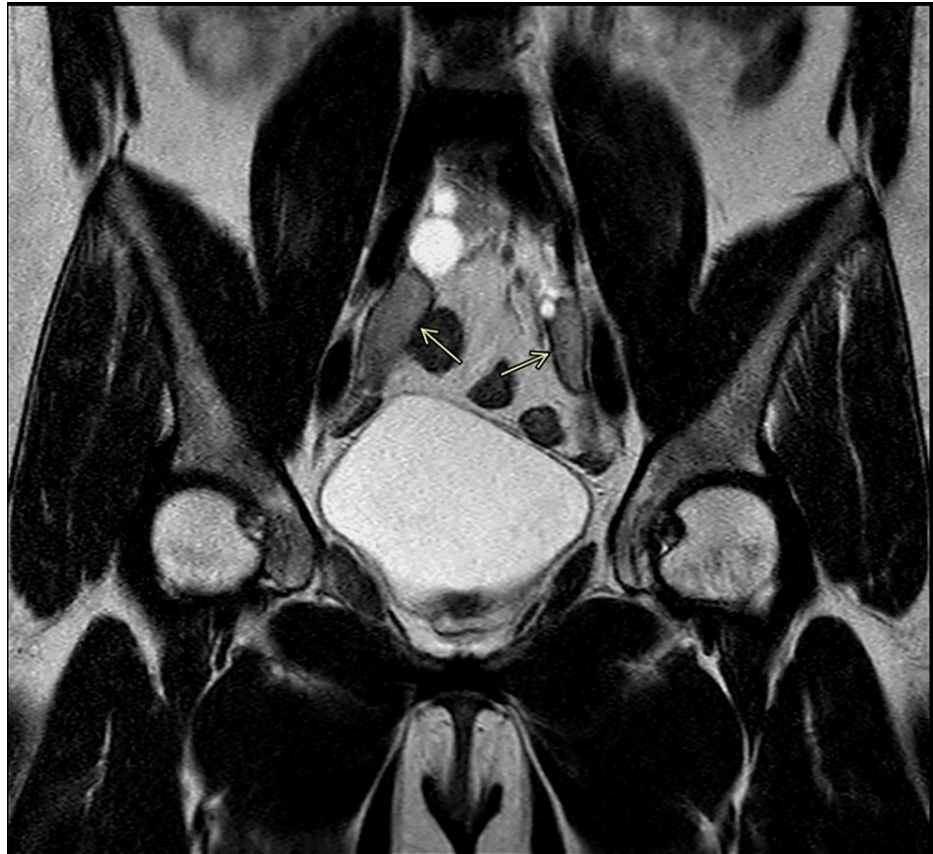


FIGURE 1: Abdominal MRI revealed oval-shaped, well-defined solid images adjacent to the bilateral iliac vessels, measuring 2.2 x 1.7 cm on the right and 2.4 x 1.0 cm on the left, potentially corresponding to male gonads

The patient underwent bilateral orchiectomy via videolaparoscopy without complications, revealing hypotrophic intra-abdominal testicles (Figure 2). The patient showed a favorable postoperative course. The anatomopathological result revealed fibrosis and azoospermia.

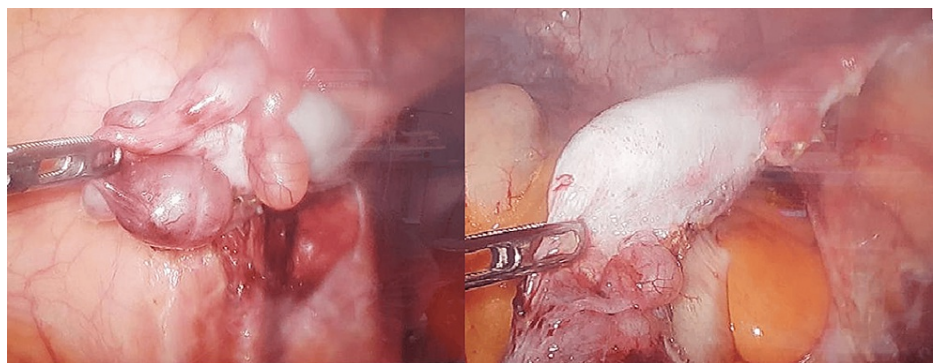


FIGURE 2: Photograph depicting hypotrophic intra-abdominal testicles

During outpatient follow-up, the patient initially presented without complaints, but in subsequent visits reported irritability, asthenia, and weight gain. Currently, the patient is undergoing endocrinological evaluation.

Discussion

CAIS, described by Morris in 1953 as the "feminizing testes syndrome," is a rare recessive genetic disorder

linked to the X chromosome. Its prevalence is approximately 1:20,000, and it is considered one of the main causes of disorders of sexual differentiation and the third cause of primary amenorrhea [3].

Until the 6th week of gestation, the embryonic gonad is undifferentiated and bipotential, meaning it contains both sets of internal genital ducts. From that point on, in individuals with normal male sexual differentiation, the testis-determining factor (SRY), present on the Y chromosome, stimulates Leydig cells (LC) to produce testosterone. This hormone acts on the Wolffian ducts (WD), which give rise to the epididymis, vas deferens, and seminal vesicles. Meanwhile, Sertoli cells (SC), under the influence of SRY, stimulate the production of anti-Müllerian hormone, leading to the regression of Müllerian ducts (MD), which would otherwise give rise to female internal organs [4,5].

The differentiation of the genital tubercle into male external genitalia begins between the 9th and 13th weeks of gestation, forming the penis, scrotal sac, and penile urethra. Its development depends on normal levels of testosterone and dihydrotestosterone (DHT), as well as functional hormonal receptors [4,5].

In patients with CAIS, there is a mutation in the androgen receptor gene (AR; X q11-q12), preventing the action of testosterone on the target organs for external male sexual differentiation. This leads to the development of the female phenotype, including the clitoris, small and large labia, and the distal portion of the vagina. It's worth noting that the regression of the Müllerian ducts does not depend on testosterone, and individuals with CAIS will not develop female internal organs (uterus, ovaries, and the upper portion of the vagina).

The clinical presentation and genital phenotype of individuals with CAIS vary, and they may exhibit mild clitoromegaly, partial fusion of the labia minora, genital ambiguity at birth, micropenis, perineal hypospadias, and cryptorchidism. In this case, the patient presented only with hypotrophic intra-abdominal testicles. From 0.8 to 2.4% of patients with a female phenotype and bilateral inguinal hernia present with CAIS [4,6].

Prepubertal diagnosis is challenging and, in most cases, occurs intraoperatively during inguinal hernia repair when the testicle is found. In patients with primary amenorrhea under investigation, imaging studies should be conducted to explore female internal organs, along with karyotyping and investigation of X-chromatin or Y-chromosome [3,4,7]. In this case, CAIS was diagnosed belatedly in an adult patient.

After the diagnosis, the timing of gonadectomy should be evaluated, discussing the risks and benefits of this procedure. In this case, there was a need for hormonal replacement therapy with testosterone due to the symptoms presented by the patient during outpatient follow-up. Considering the high risk of gonadal malignancy (25%) in these cases, surgical treatment in the present report was the best option [8,9].

Conclusions

Complete androgen insensitivity syndrome is an uncommon condition, and its diagnosis should be made as early as possible due to the risk of gonadal malignancy. Considering that after surgical treatment, hormonal replacement is necessary since the patient will develop hypogonadism.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Luís Cesar Fava Spessoto, Júlia Saraiva Avelino Silveira, Andres Menacho Abularach, Gustavo Santana Garcia, Matheus Castro Almeida, Guilherme Cerqueira Gonzales, Ana Clara Nagle Spessoto, Fernando Nestor Facio Jr., Mateus Henrique Silva Faria

Acquisition, analysis, or interpretation of data: Luís Cesar Fava Spessoto, Andres Menacho Abularach, Matheus Castro Almeida, Guilherme Cerqueira Gonzales, Ana Clara Nagle Spessoto, Fernando Nestor Facio Jr., Mateus Henrique Silva Faria

Drafting of the manuscript: Luís Cesar Fava Spessoto, Júlia Saraiva Avelino Silveira, Andres Menacho Abularach, Matheus Castro Almeida, Guilherme Cerqueira Gonzales, Ana Clara Nagle Spessoto, Fernando Nestor Facio Jr., Mateus Henrique Silva Faria

Critical review of the manuscript for important intellectual content: Luís Cesar Fava Spessoto, Andres Menacho Abularach, Gustavo Santana Garcia, Ana Clara Nagle Spessoto, Mateus Henrique Silva Faria

Supervision: Luís Cesar Fava Spessoto, Andres Menacho Abularach, Mateus Henrique Silva Faria

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

Acknowledgements

The authors would like to thank the staff of the Radiology Unit of Hospital de Base/FUNFARME for the radiological analysis.

References

1. Muroso K, Mendonca BB, Arnhold IJ, Rigon AC, Migeon CJ, Brown TR: Human androgen insensitivity due to point mutations encoding amino acid substitutions in the androgen receptor steroid-binding domain. *Hum Mutat.* 1995, 6:152-162. [10.1002/humu.1380060208](https://doi.org/10.1002/humu.1380060208)
2. Warne GL: Complete androgen insensitivity syndrome: a guide for parents and patients . In: *Disorders of Sex Development*. Hutson J, Warne G, Grover S (ed): Springer, Berlin; 2012. 291-298. [10.1007/978-3-642-22964-0_27](https://doi.org/10.1007/978-3-642-22964-0_27)
3. Melo KF, Mendonça BB, Billerbeck AE, Costa EM, Latronico AC, Arnhold IJ: Androgen insensitivity syndrome: clinical, hormonal and molecular analysis of 33 cases [Article in Portuguese]. *Arq Bras Endocrinol Metabol.* 2005, 49:87-97. [10.1590/s0004-27302005000100012](https://doi.org/10.1590/s0004-27302005000100012)
4. Quigley CA, de Bellis A, Marschke KB, El-Awady MK, Wilson EM, French FS: Androgen receptor defects: historical, clinical, and molecular perspectives. *Endocr Rev.* 1995, 16:271-321. [10.1210/edrv-16-3-271](https://doi.org/10.1210/edrv-16-3-271)
5. Kupfer SR, Quigley CA, French FS: Male pseudohermaphroditism. *Semin Perinatol.* 1992, 16:319-331.
6. Sarpel U, Palmer SK, Dolgin SE: The incidence of complete androgen insensitivity in girls with inguinal hernias and assessment of screening by vaginal length measurement. *J Pediatr Surg.* 2005, 40:133-137. [10.1016/j.jpedsurg.2004.09.012](https://doi.org/10.1016/j.jpedsurg.2004.09.012)
7. Andrade FP, Cabrera PM, Cáceres F, Gil B, Rodríguez-Barbero JM, Angulo JC: Umbilical KeyPort bilateral laparoscopic orchiectomy in patient with complete androgen insensitivity syndrome. *Int Braz J Urol.* 2012, 38:695-700. [10.1590/s1677-55382012000500016](https://doi.org/10.1590/s1677-55382012000500016)
8. Freitas F, Souza C, Salazar C: Pseudo-hermafroditismo masculino. *J da Soc Bras de Ginecol Endóc.* 2001, 8:2-5.
9. Corrêa RV, Wey JC, Billerbeck AE, Melo KF, Mendonça BB, Wey MV, Arnhold IJ: Complete form of androgen insensitivity syndrome in Brazilian patients due to P766A mutation in the androgen receptor [Article in Portuguese]. *Arq Bras Endocrinol Metabol.* 2005, 49:98-102. [10.1590/s0004-27302005000100013](https://doi.org/10.1590/s0004-27302005000100013)