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CASE REPORT

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New mutation causing androgen insensitivity syndrome – a case report and review of literature

Marzena Maciejewska-Jeske[a]*, Patrycja Rojewska-Madziala[a]*, Karolina Broda[b], Karolina Drabek[b], Anna Szeliga[a], Adam Czyzyk[a], Stanislaw Malinger[c], Anna Kostrzak[a], Agnieszka Podfigurna[a], Gregory Bala[b], Blazej Meczekalski[a], Agnieszka Malcher[d]* and Maciej Kurpisz[d]*

[a]Department of Gynecological Endocrinology, Poznan University of Medical Sciences, Poznan, Poland; [b]Students Scientific Society of the Department of Gynecological Endocrinology, Poznan University of Medical Sciences, Poznan, Poland; [c]Department of General and Endocrine Surgery and Gastroenterological Oncology, Poznan University of Medical Sciences, Poznan, Poland; [d]Department of Reproductive Biology and Stem Cells, Institute of Human Genetics, Polish Academy of Sciences, Poznan, Poland

ABSTRACT

Androgen insensitivity syndrome (AIS) is a congenital disorder in which a defect in the androgen receptor (AR) gene leads to cellular resistance to androgens. Defects in the AR gene, located on the X chromosome, result in the development of a feminine phenotype in chromosomally male (46, XY) individuals. In this case report, we present a 44 years old patient with complete androgen insensitivity syndrome (CAIS) initially presenting with primary amenorrhea. The patient underwent a full clinical evaluation, revealing hypoplastic vagina and a lack of uterus and ovaries. Hormonal evaluation revealed markedly elevated testosterone, FSH, and LH serum concentrations. Diagnostic imaging, including pelvic MRI, confirmed the presence of two solid masses in the inguinal canals (right 26 × 13 mm, left 25 × 15 mm). The patient underwent genetic testing, revealing a 46 XY karyotype and an as of yet unprecedented androgen receptor mutation. The type of the mutation was a single-base exchange – the substitution from cytosine to thymine in chromosome X:66942710 position (referred to human reference genome GRCh37), which has resulted in an amino acid changes from leucine (CTT) to phenyloalanine (TTT) in ligand-binding domain.

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Introduction

Androgen insensitivity syndrome (AIS), first described by Morris in 1953, is a congenital disorder manifesting as a result of cellular resistance to androgens [1]. The pathogenesis of AIS involves a defect in the androgen receptor gene located on the X chromosome and results in the development of a feminine phenotype in a genetically male (46, XY) individual [2]. Three clinical phenotypes of AIS are observed, relating to the degree of androgen insensitivity: Complete androgen insensitivity syndrome (CAIS) exhibits typical female genitalia, partial androgen insensitivity syndrome (PAIS) is associated with predominantly female or ambiguous genitalia, and mild androgen insensitivity syndrome (MAIS) [2]. PAIS is most often the result of missense mutations in the androgen receptor gene and causes the mildest forms of AIS [3]. In contrast, CAIS manifests as the most complete form of AIS. The female phenotype observed in CAIS is the result of mutations in cellular receptors causing incapacitation and absolute resistance to testosterone and DHT. Primordial testis continues to produce anti-Müllerian hormone, thus suppressing the formation of female internal reproductive organs and leading to primary amenorrhea in adolescence. The lack of androgen stimulation concurrently limits differentiation to proper male external genitalia and virilization [3,4].

Case report

A 44 years old Caucasian female was referred to the Department of Gynecological Endocrinology, Poznan University of Medical Sciences, after presenting to her primary care provider with a chief complaint of primary amenorrhea. She had no relevant past medical or family history and had never requested diagnostic workups prior to admission. Her weight upon admission was 98 kg, height 164 cm, and BMI 36.5 kg/m^2. The patient had no axillary hair and poorly developed secondary sex characteristics (Tanner stage 3 breast development and Tanner stage 1 pubic hair). Her external genitalia appeared normal. Gynecological examination and transvaginal ultrasound revealed a hypoplastic vagina ending blindly with a depth of 3 cm and a complete lack of uterus and ovaries. Urography revealed no abnormalities of the urinary tract.

Hormonal evaluation

Hormonal evaluation in fasting blood was made using an enzyme-linked immunosorbent assay. Serum follicle stimulating hormone, luteinizing hormone, and testosterone concentration were markedly elevated, while estradiol serum concentration was significantly decreased. The other hormonal results were within normal limits (Table 1). Taking into consideration above results, the suspicion of AIS was made.

Diagnostic imaging

A pelvic MRI was performed to investigate the apparent lack of internal female genital organs. The absence of an uterus and

CONTACT Blazej Meczekalski blazejmeczekalski@yahoo.com Department of Gynecological Endocrinology, Poznan University of Medical Sciences, 33 Polna Street 60-535 Poznan, Poland
*These authors equally contributed to this work.

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ovaries was confirmed, while an adequately developed distal vagina was also noted. MRI did not reveal any additional pathology or masses within the pelvis. An ultrasound of the inguinal canals was then performed and revealed the presence of two oval homogenously echogenic structures bilaterally below the superficial inguinal rings (right 37 × 15 × 26 mm, left 28 × 14 × 19 mm). A follow-up contrast enhanced pelvic MRI was explicitly performed to visualize the inguinal canals. Two homogenous contrast-enhancing solid mass lesions were confirmed bilaterally in the distal canals (right 26 × 13 mm, left 25 × 15 mm). It was determined that these lesions most likely corresponded to undescended testes.

On the basis of this clinical picture, biochemical parameters, and diagnostic imaging, the patient was referred to the Department of General, Gastroenterological, and Endocrine Surgery, Poznan University of Medical Sciences and underwent surgical excision of both inguinal masses.

Histopathological examination

Seminiferous tubules located in excised gonads contained only Sertoli cells. There were numerous Leydig cells in the stroma. Within the right gonad, the nodule composed of hypoplastic seminiferous tubules with immature Sertoli and Leydig cells was present (Sertoli-Leydig hamartoma). The whole microscopic image corresponded to the clinical diagnosis: AIS.

Molecular assessment

Chromosomal analysis (using GTG banding) confirmed a 46, XY karyotype. To confirm the diagnosis of AIS and to subsequently identify the androgen receptor gene mutation responsible, genetic testing was performed by the Institute of Human Genetics, Polish Academy of Sciences, Poznan, Poland.

We have sequenced the coding AR region. The reaction mixture for sequencing contained 15–30 ng of DNA, 1 µl of AR primer (20 µM), 2 µl of BigDye (5x) buffer, and BigDye Terminator v3.1 (Applied Biosystems, Life Technologies, Carlsbad, CA, USA) in a final volume of 20 µl. The primer pairs used for the sequencing of exon 7 of AR were forward-5′-GGCATGCTTCCCCTCCCC ATTC-'3; reverse 5'TGCTTACAGGCTGCACGGAGTC-'3. The products were separated on an ABI Prism 310 (Applied Biosystems, Life Technologies, Carlsbad, CA, USA). Changes in the sequenced AR fragment of the patient were located with respect to the reference DNA (made available in the database of the NCBI) using CLC program Workbench 6.0. The comparison of the AR sequence of given individual was performed according to the NCBI Reference Sequence NM_000044.3.

The type of the mutation was a single-base exchange – the substitution from cytosine to thymine in chromosome X:66942710 position (referred to human reference genome GRCh37).

The mutated variant was neither found in ExAC nor in 1000 G, but the identified mutation predicted pathological effect in Mutation Taster web application (http://www.mutationtaster.org/).

Further treatment

The patient we present has, leading up to the present investigation, led a well-adjusted life as a woman and is a fully functioning member of society. She never underwent vaginal reconstruction or other cosmetic surgeries. Following the excision of both testes, she agreed to start hormone replacement therapy. Owing to the absence of a uterus, combination therapy with progestin was deemed unnecessary and monotherapy (estradiol 2 mg per os daily) was started. Serum FSH and E2 concentrations were measured at one-year follow-up post-surgery (FSH 14.3 mlU/mL and E2 83.34 pg/mL), and anti-Müllerian hormone (AMH) was also measured at that time (AMH 0.01 ng/mL) (Table 1). The patient remains under ambulatory care at The Department of Gynecological Endocrinology, Poznan University of Medical Sciences.

Table 1. Serum concentrations of chosen hormone and biochemical markers in described patient at the moment of diagnosis and after surgical removal of gonads.

	At diagnosis	After surgery; on HRT	Reference values
FSH [mIU/mL]	70.47	14.3	3.5–12.5
LH [mIU/mL]	68.77	11.27	2.4–12.6
Estradiol [pg/mL]	39.0	83.34	12.5–166
Testosterone [ng/mL]	5.29	1.31	0.06–0.82
DHEA-S [µmol/L]	5.19	11.9	1.65–9.15
TSH [µIU/mL]	0.41	0.3	0.27–4.2
fT4 [ng/dL]	1.27	1.62	0.93–1.7
Insulin [mU/mL]	4.88	4.45	2.6–24.9
Glucose [mg/dl]	94.8	84.4	55–99
TC [mg/dL]	144.3	158.2	<190
HDL [mg/dL]	46.2	41.1	>45
LDL [mg/dL]	88.7	104.4	<115
TG [mg/dL]	46.8	63.7	<150
AMH [ng/mL]		<0.01	

TC: total cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TG: triglycerides.

Discussion

CAIS, formerly known as Morris syndrome or testicular feminization syndrome, occurs in 1 out of 20,000 births and is regarded as the third most common cause of primary amenorrhea [5,6]. In this paper, we report on the case of a 44-year-old patient diagnosed with CAIS following her initial presentation with primary amenorrhea.

Recent discussions in the literature postulate that a diagnosis of AIS can be made prenatally in cases where a karyotype obtained from amniotic fluid contradicts sex-determining observations by ultrasonography. Most cases of CAIS, however, are unrecognized at birth and continue to go unnoticed throughout childhood due to the unambiguously female phenotype of the infant. On rare occasions when discovered in infancy, inguinal hernias or testes in the inguinal canals in a female patient are the first hint at the diagnosis [6]. Otherwise, screening for CAIS is difficult and often only considered when delayed puberty or primary amenorrhea is observed in adolescence [7,8].

CAIS is an X-linked disease manifesting as a result of the impaired functioning of cellular androgen receptors. Despite possessing a male karyotype, affected patients develop a female habitus, short and blind-ended vagina, the absence of uterus and ovaries, and normal-appearing testes which do not descend. These structurally normal testes may instead be found anywhere along the embryonic path of testicular descent [9]. In adolescence, regular breast development and a lack of pubic and axillary hair is observed, while stature approaches the expected mean male height [10,11]. While certain characteristics such as lack of pubic and axillary hair are a consequence of androgen insensitivity during puberty, the absence of structures developing from the Müllerian ducts arise from prenatal hormone abnormalities [5]. Elevated anti-Müllerian hormone (AMH) levels are typical for infant males [12]. Low levels of LH and T are

characteristic for male newborns and infants, increasing significantly after puberty [13,14].

The androgen receptor (AR) gene is located proximally on the long arm of chromosome X (locus Xq11-12) [15]. It encodes a transcription factor containing three major functional domains: the ligand-binding domain, the DNA-binding domain, and the N-terminal domain [16]. Over 1000 mutations causing AIS have been identified in the AR gene. Most of these are missense mutations, with numerous splicing mutations as well. Insertion and deletion mutations are relatively rare at this site [16]. In our case, chromosome analysis using GTG method was carried out. It revealed 46, XY karyotype with a single-base exchange in AR gene, which was the substitution from cytosine to thymine in chromosome X:66942710 position (referred to human reference genome GRCh37) which has resulted in an amino acid changes from leucine (CTT) to phenyloalanine (TTT) in ligand-binding domain. Recently, several new mutations in the AR gene have been reported and linked to AIS. Wu *et al.* reported four new mutations (insertions and deletions) in exons 1, 6, and 8 (c.1368_1369insGGCGGC, c.1436delC, c.2440_2441delTT, c.2633_2634insAGTTCAC) [17]. Similarly, Wang *et al.* discovered a new splice acceptor site mutation (c(0).1769-1G > C) [18].

The patient we present exhibits a complete picture of CAIS [6]. Both gynecological examination and transvaginal ultrasound revealed a hypoplastic vagina, and the absence of both uterus and ovaries. The external genitalia were normal. Many accounts of CAIS in the literature also describe irregular labia, bilateral inguinal hernias, and breast asymmetry [5,19,20]; however, no such additional findings were observed in this patient. Only on ultrasound examination of the inguinal canals were aberrant structures, later confirmed to be testes, discovered in the superficial inguinal rings.

Upon admission, the hormone profile of our patient mirrored that was described in the literature. Post-pubertal patients presenting with CAIS and before orchidectomy often have increased serum-luteinizing hormone and testosterone. LH and T in our patient was 68.77 mIU/mL (norm: 1.4–21 mIU/mL) and 5.29 ng/mL (norm: .06–.82 ng/mL), respectively. Interestingly, serum E2 concentration was noted to be decreased (39 pg/mL) prior to orchidectomy. Patients with CAIS generally have significantly elevated T concentrations, with both T and E2 often reaching the normal expected reference level for men. E2 levels in this patient were well below both female and male reference levels. Typically, FSH levels are within normal male range due to down-regulation by inhibin which is produced by Sertoli cells in the testes. Rarely is it above the normal range, as in our patient, suggesting a possible decline in this inhibitory effect. Following gonadectomy in post-pubertal CAIS patients, FSH and LH increase due to the loss of negative feedback from the gonads. These gonadotropins decrease once again after starting HRT [20,21].

It is still unclear as to the optimal time for a patient to undergo orchidectomy. Testosterone produced by the testes does, via peripheral aromatization, provide adequate estrogen to undergo puberty [5]. However, the risk of testicular malignancy is greatly elevated, especially if the testes remain in the abdomen [22]. The risk of malignancy in undescended intra-abdominal testes increases from 3.6% at the age of 25 to 33% at the age of 50 [23]. Cools *et al.* report the risk of carcinoma *in situ* (CIS) to be around 10% in adults with CAIS. The *Gonadoblastoma on Y* (*GBY*) region, located proximally on the short arm of the Y chromosome, is considered to be a main genetic factor behind malignant germ cell proliferation. The *TSPY* (*testis-specific protein, Y-linked*) region within *GBY* is considered an oncogene associated with carcinogenesis of the testes. Physiologically, *TSPY* enhances mitotic proliferation of germ cells. Recent findings suggest it is this expression that is up-regulated in CAIS [24].

Regarding high rates of CIS, gonadoblastoma, and other germ cell tumors in AIS patients, additional test should be performed for malignancy exclusion. Octamer-binding transcription factor (OCT 3/4) and placental-like alkaline phosphatase (PLAP) immunostaining in excised gonads seem to be helpful in the differential diagnosis of testicular neoplasms that are difficult to distinguish on histopathological examination [22,25,26].

In the absence of contraindications, patients suffering from CAIS who undergo gonadectomy should begin hormonal replacement therapy. Treatment with HRT will maintain secondary sexual characteristics and prevent against osteoporosis and coronary heart disease. CAIS patients commonly suffer from osteopenia and should have bone mineral density screened using dual-energy X-ray absorptiometry (DEXA). Although improvement in bone density is often seen while on HRT, achieving normal values is impossible in most cases [27]. When secondary sexual characteristics are improperly developed, a higher dose of estradiol will encourage the gradual induction of maturation [4]. At 44 years old, the patient we present was decidedly post-pubertal. As such, a standard oral daily dose of 2 mg 17β-estradiol was initiated.

Continued care for CAIS patients requires a multi-pronged approach, addressing psychological and sexual issues. Patients often continue to lead normal socially integrated lives as fully functioning women but commonly report psychological issues. Although gender identity is not a common concern among these patients, some reports distress with respect to the morphology of their sexual organs. Infertility is also a significant factor leading to psychological distress [28,29]. Studies often highlight a lack of sexual satisfaction and self-confidence in the CAIS population. Decreased libido or dyspareunia are often emphasized as being decisive disturbances in sexual life [30]. Following vaginoplasty however, many AIS patients report amelioration of sexual life, improved ability to reach orgasm, and increased libido [31].

In this case report, we presented a 44-year-old patient suffering from CAIS as the result of a new mutation of the androgen receptor gene: a single-base pair substitution from cytosine to thymine at position X:66942710.

Disclosure statement

No potential conflict of interest was reported by the authors.

References

[1] Morris JM. The syndrome of testicular feminization in male pseudohermaphrodites. Am J Obstet Gynecol. 1953;65:1192–1211.
[2] Mongan NP, Tadokoro-Cuccaro R, Bunch T, et al. Androgen insensitivity syndrome. Best Pract Res Clin Endocrinol Metab. 2015;29:569–580.
[3] Gulía C, Baldassarra S, Zangari A, et al. Androgen insensitivity syndrome. Eur Rev Med Pharmacol Sci. 2018;22:3873–3887.
[4] Batista RL, Costa EMF, Rodrigues AS, et al. Androgen insensitivity syndrome: a review. Arch Endocrinol Metab. 2018;62:227–235.
[5] Gîngu C, Dick A, Pătrăşcoiu S, et al. Testicular feminization: complete androgen insensitivity syndrome. Discussions based on a case report. Rom J Morphol Embryol 2014;55:177–181.
[6] Ross GT. Disorders of the ovary and female reproductive tract. In: Williams Textbook of Endocrinology, Wilson JD, Foster DW (Eds), Saunders, Philadelphia 1985. p. 206.

[7] Souhail R, Amine S, Nadia A, et al. Complete androgen insensitivity syndrome or testicular feminization: review of literature based on a case report. Pan Afr Med J. 2016;25:199.
[8] Jung EJ, Im DH, Park YH, et al. Female with 46, XY karyotype. Obstet Gynecol Sci. 2017;60:378–382.
[9] Oakes MB, Eyvazzadeh AD, Quint E, et al. Complete androgen insensitivity syndrome – a review. J Pediatr Adolesc Gynecol. 2008; 21:305–310.
[10] Wilkins L. The diagnosis and treatment of endocrine disorders in childhood and adolescence. Charles C Thomas Pub Ltd, Springfield, IL 1957;258.
[11] Papadimitriou DT, Linglart A, Morel Y, et al. Puberty in subjects with complete androgen insensitivity syndrome. Horm Res Paediatr. 2006;65:126–131.
[12] Dodge ST, Finkelston MS, Miyazawa K. Testicular feminization with incomplete Müllerian regression. Fertil Steril. 1985;43:937–938.
[13] Ahmed SF, Achermann JC, Arlt W, et al. UK guidance on the initial evaluation of an infant or an adolescent with a suspected disorder of sex development. Clin Endocrinol. 2011;75:12–26.
[14] Bouvattier C, Carel J-C, Lecointre C, et al. Postnatal Changes of T, LH, and FSH in 46, XY infants with mutations in the AR gene. J Clin Endocrinol Metab 2002;87:29–32.
[15] Lubahn DB, Joseph DR, Sullivan PM, et al. Cloning of human androgen receptor complementary DNA and localization to the X chromosome. Science. 1988;240:327–330.
[16] Yuan S-M, Huang H, Tu C-F, et al. A rare polypyrimidine tract mutation in the androgen receptor gene results in complete androgen insensitivity syndrome. Asian J Androl. 2018;20:308.
[17] Wu Q, Wang C, Shi H, et al. Identification of 4 novel mutations of androgen receptor gene in 8 Chinese families with complete androgen insensitivity syndrome. Clin Genet. 2018;94(2):269–270.
[18] Wang S, Xia P, Cacalano NA, et al. Complete androgen insensitivity syndrome caused by c.1769-1G > C mutation and activation of a cryptic splice acceptor site in the androgen receptor gene. Steroids. 2018;137:64–69.
[19] Ataya KM, Mroueh AM. Urologic anomalies associated with an absent uterus. J Urol. 1982;127:1125–1127.
[20] Melo KFS, Mendonca BB, Billerbeck AEC, et al. Clinical, hormonal, behavioral, and genetic characteristics of androgen insensitivity syndrome in a Brazilian cohort: five novel mutations in the androgen receptor gene. J Clin Endocrinol Metab. 2003;88:3241–3250.
[21] Doehnert U, Bertelloni S, Werner R, et al. Characteristic features of reproductive hormone profiles in late adolescent and adult females with complete androgen insensitivity syndrome. Sex Dev. 2015;9: 69–74.
[22] Kathrins M, Kolon TF. Malignancy in disorders of sex development. Transl Androl Urol. 2016;5:794–798.
[23] Manuel M, Katayama PK, Jones HW. The age of occurrence of gonadal tumors in intersex patients with a Y chromosome. Am J Obstet Gynecol. 1976;124:293–300.
[24] Cools M, Looijenga L. Update on the pathophysiology and risk factors for the development of malignant testicular germ cell tumors in complete androgen insensitivity syndrome. Sex Dev. 2017;11:175–181.
[25] Kommoss F, Oliva E, Bittinger F, et al. Inhibin-α, CD99, HEA125, PLAP, and chromogranin immunoreactivity in testicular neoplasms and the androgen insensitivity syndrome. Hum Pathol. 2000;31: 1055–1061.
[26] Aliberti P, Perez Garrido N, Marino R, et al. Androgen insensitivity syndrome at prepuberty: marked loss of spermatogonial cells at early childhood and presence of gonocytes up to puberty. Sex Dev. 2017; 11:225–237.
[27] Bertelloni S, Meriggiola MC, Dati E, et al. Bone mineral density in women living with complete androgen insensitivity syndrome and intact testes or removed gonads. Sex Dev. 2017;11:182–189.
[28] Fliegner M, Krupp K, Brunner F, et al. Sexual life and sexual wellness in individuals with complete androgen insensitivity syndrome (CAIS) and Mayer-Rokitansky-Küster-Hauser syndrome (MRKHS). J Sex Med. 2014;11:729–742.
[29] Poláková M, Alexander D, Sulc J, et al. Pregnancy and delivery in a patient with pure 46, XY karyotype. Summary of actual knowledge about XY women. Ces Gynekol. 2013;78:443–447.
[30] Köhler B, Kleinemeier E, Lux A, et al. Satisfaction with genital surgery and sexual life of adults with XY disorders of sex development: results from the German clinical evaluation study. J Clin Endocrinol Metab. 2012;97:577–588.
[31] Wisniewski AB, Migeon CJ, Meyer-Bahlburg HFL, et al. Complete androgen insensitivity syndrome: long-term medical, surgical, and psychosexual Outcome. J Clin Endocrinol Metab. 2000;85:2664–2669.