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Case Report

Late Recognition of Aromatase Deficiency Following 16 Years of Misdiagnosis as Congenital Adrenal Hyperplasia: A Case with Coexisting Gonadoblastoma and Dysgerminoma

Alfadhli E and Turkistani A. Aromatase Deficiency and Gonadal Tumors

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Abstract
Aromatase deficiency (AD) is a rare autosomal recessive disorder caused by pathogenic variants in the CYP19A1 gene, resulting in impaired conversion of androgens to estrogens. Clinical manifestations in 46, XX individuals include ambiguous genitalia, delayed puberty, and reproductive dysfunction. Both sexes may develop metabolic abnormalities, delayed epiphyseal closure, eunuchoid body proportions, and low bone mass. Because of its rarity and overlap with congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21OHD), diagnosis may be delayed or missed. Gonadal tumors have not been reported in association with AD. We describe a 20-year-old female with ambiguous genitalia at birth who was diagnosed in infancy with 21OHD and treated with hydrocortisone and fludrocortisone. Despite poor treatment adherence, she never developed adrenal insufficiency. At 16 years of age, she was referred for evaluation of primary amenorrhea and absent puberty. Assessment revealed hypergonadotropic hypogonadism with markedly low estradiol levels, normal basal and ACTH-stimulated 17-hydroxyprogesterone levels (17-OHP), and a 46, XX karyotype, findings that were inconsistent with CAH. Additional features included metabolic abnormalities and low bone mass. Whole-genome sequencing identified a homozygous pathogenic CYP19A1 splice-site variant (c.1263+1G>T), confirming AD. Imaging and surgery demonstrated an enlarged right adnexal mass and a hypoplastic left ovary. Histopathology revealed bilateral gonadoblastoma with dysgerminoma arising in the right ovary. This case highlights the diagnostic challenges of AD and emphasizes the importance of reconsidering a diagnosis of CAH when biochemical findings are discordant with the clinical picture. To our knowledge, this is the first reported case of genetically confirmed aromatase deficiency with coexisting gonadoblastoma and dysgerminoma. Whether this coexistence represents a causal association or a coincidental finding remains uncertain.
Keywords: Aromatase deficiency; Congenital adrenal hyperplasia; CYP19A1 gene; Dysgerminoma; Gonadoblastoma

What is already known on this topic?
Aromatase deficiency is a rare disorder caused by CYP19A1 variants that impair estrogen synthesis. In 46, XX individuals, it may present with ambiguous genitalia, delayed puberty, primary amenorrhea, and can be mistaken for CAH.

What this study adds?
This case highlights a 16-year delay in the diagnosis of AD due to misdiagnosis as 21OHD and emphasizes the importance of reassessing the diagnosis when biochemical findings are discordant. It also describes the coexistence of gonadoblastoma and dysgerminoma in a patient with AD a previously unreported observation that warrants further investigation.

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Introduction
Aromatase deficiency (AD) is a rare autosomal recessive disorder caused by loss-of-function variants in the CYP19A1 gene, which encodes the aromatase enzyme responsible for the conversion of androgens to estrogens. Aromatase is expressed in multiple tissues, including the ovaries, testes, adipose tissue, bone, and brain, and plays a critical role in sexual development, skeletal maturation, reproductive function, and metabolic homeostasis [1,2]. Since the first description of aromatase deficiency in 1991 in a Japanese newborn girl with a defect in the aromatase gene [3], numerous cases have been reported worldwide, expanding the phenotypic and genetic spectrum of the disorder [4]. Deficient aromatase activity results in profound estrogen deficiency with disrupted estrogen–androgen balance, producing a broad spectrum of clinical manifestations that vary according to sex and age at presentation [1,2,4,5]. In 46,XX individuals, the disorder typically presents with prenatal virilization of the external genitalia due to excess androgen exposure during fetal development, while internal Müllerian structures are preserved. Transient maternal virilization during pregnancy has also been recognized, reflecting placental inability to convert fetal androgens into estrogens [6]. During adolescence, affected females typically develop delayed puberty, absent or incomplete breast development, primary amenorrhea, and hypergonadotropic hypogonadism [1,2,4,5]. In both males and females, chronic estrogen deficiency impairs epiphyseal closure and bone mineralization, leading to continued linear growth, tall stature, delayed bone age, reduced bone mass, and metabolic abnormalities including obesity, insulin resistance, and dyslipidemia [1,2,4,5]. Despite its distinctive biochemical profile, AD remains an important diagnostic challenge because of its rarity and overlap with other disorders of sex development, particularly CAH in virilized 46,XX infants. Early recognition is essential to allow timely hormone replacement and prevention of long-term skeletal, reproductive, and metabolic complications. We report a genetically confirmed case of AD that remained unrecognized until late adolescence and was subsequently diagnosed with coexisting

gonadoblastoma and dysgerminoma. To our knowledge, this is the first reported case of genetically confirmed AD with coexisting gonadoblastoma and dysgerminoma. Whether this coexistence represents a causal relationship or a coincidental finding remains uncertain.

Case Presentation

A 20-year-old female born with ambiguous genitalia was initially diagnosed during infancy with CAH due to presumed 21OHD and subsequently underwent corrective genital surgery, resulting in a normal female external genital phenotype. Historical information regarding the neonatal presentation was obtained from a referral report prepared by the adult endocrinologist following referral from pediatric care, as the original pediatric records were unavailable. According to this report, the patient initially presented at 11 days of age with clitoromegaly, hyperpigmented fused labioscrotal folds, a urethral opening at the base of the phallus, and non-palpable gonads. She subsequently underwent two-stage genital reconstructive surgery during infancy; however, the operative report could not be retrieved. The referral report documented neonatal findings of an elevated initial 17-OHP level, normal serum electrolytes, and a 46,XX karyotype, although detailed quantitative laboratory results were not available. She was treated with hydrocortisone and fludrocortisone from infancy onward; however, medication adherence was poor throughout follow-up.

The patient remained under regular pediatric endocrinology follow-up throughout childhood and adolescence. At the age of 16 years, following transition to adult endocrinology care, the diagnosis was re-evaluated because her clinical course and biochemical findings were inconsistent with CAH. She presented with primary amenorrhea, absent secondary sexual characteristics, continued linear growth, and weight gain.

Family history was notable for parental consanguinity. The patient had five siblings, including one sister who attained menarche at 14 years of age. There was no reported history of ambiguous genitalia, delayed puberty, or reproductive disorders among the siblings. The presence or absence of maternal virilization during pregnancy could not be ascertained, as the mother was unable to reliably recall symptoms from that period.

On physical examination at presentation to our center, she weighed 82 kg and measured 156 cm in height (BMI 33.7 kg/m²), with a blood pressure of 126/64 mmHg. Notable features included central adiposity, acanthosis nigricans, and red abdominal striae. Secondary sexual characteristics were underdeveloped, with Tanner stage B1 breasts (adipose tissue only) and sparse pubic and axillary hair. There were no clinical features of hyperandrogenism. External genitalia demonstrated a normal female phenotype following previous reconstructive surgery. At the most recent follow-up, her height had increased to 164 cm and her weight to 96 kg (BMI 35.7 kg/m²), demonstrating continued linear growth into adulthood.

A comprehensive hormonal and metabolic evaluation revealed marked hypergonadotropic hypogonadism, with significantly elevated FSH and LH levels accompanied by profoundly low estradiol indicating primary ovarian failure. Testosterone levels were within the normal female reference range (Table 1).

At presentation, the patient had not taken her prescribed hydrocortisone and fludrocortisone for approximately one week because of poor treatment adherence. Despite being off treatment, serum sodium, potassium, plasma renin, and ACTH levels remained within the normal range (Table 1). A standard short ACTH stimulation test (cosyntropin) was therefore performed while she was off glucocorticoid and mineralocorticoid therapy. The cortisol response was appropriate, demonstrating an adequate stimulated cortisol response and excluding adrenal insufficiency. Basal and stimulated 17-OHP levels remained within the normal range, effectively excluding 21OHD. Detailed cortisol and 17-OHP results are summarized in Table 2.

Metabolic assessment demonstrated prediabetes (HbA1c 6.0%) and an atherogenic lipid profile characterized by elevated total cholesterol, LDL cholesterol, and triglycerides, with mildly reduced HDL cholesterol. These findings are consistent with the endocrine and metabolic consequences of chronic estrogen deficiency associated with AD. Serum tumor markers, including β-human chorionic gonadotropin (β-hCG), alpha-fetoprotein (AFP), and cancer antigen 125 (CA-125), were within the normal range. Detailed laboratory results are summarized in Table 1.

Chromosomal analysis revealed a female karyotype, 46, XX, without detectable chromosomal abnormalities. Whole-genome sequencing identified a homozygous pathogenic CYP19A1 splice-site variant (c.1263+1G>T; chr15:51212319:C>A, GRCh38), classified as pathogenic according to ACMG criteria.

Segregation analysis of the identified CYP19A1 variant demonstrated autosomal recessive inheritance within the family. The parents, who are first cousins, were both heterozygous carriers of the pathogenic CYP19A1 variant. Of their six children, three—including the index patient and two brothers—were homozygous for the pathogenic variant, two were heterozygous carriers, and one tested negative for the familial variant (Figure 1).

Additional investigations further characterized the patient's phenotype. Bone age assessment of the left hand and wrist revealed a bone age of approximately 12 years despite a chronological age of 20 years, with persistent open epiphyseal growth plates (Figure 2). Dual-energy X-ray absorptiometry (DXA) demonstrated low bone mineral density for age, with a lumbar spine Z-score of −4.3 and a left femoral neck Z-score of −1.7.

Pelvic MRI demonstrated a markedly hypoplastic uterus (5 × 8 × 26 mm) and vagina and a right adnexal mass measuring 3.5 × 5.7 × 4.9 cm. The right ovary was not separately visualized and was considered likely replaced by the adnexal lesion, while the left ovary and fallopian tube were not identified. Diagnostic laparoscopy demonstrated a markedly hypoplastic uterus, a streak-like left ovary, and a right adnexal mass involving the right ovary, from which a biopsy was obtained. The cervix and vaginal canal were not visualized intraoperatively. Histopathological examination of the biopsy demonstrated gonadoblastoma. Based on these findings, the patient subsequently underwent bilateral salpingo-oophorectomy with pelvic lymph node sampling. Histopathological examination demonstrated a 0.7-cm dysgerminoma arising in a background of gonadoblastoma in the right ovary, while the left ovary contained foci of gonadoblastoma. One pelvic lymph node contained isolated tumor cells, and the final pathological stage was FIGO stage IA (pT1a N0(i+), AJCC 8th edition). Postoperative PET-CT demonstrated FDG-avid retroperitoneal and pelvic lymphadenopathy suspicious for metastatic disease, without evidence of distant metastases. Following multidisciplinary oncology review, adjuvant chemotherapy with bleomycin, etoposide, and cisplatin (BEP) was recommended based on the suspicious postoperative PET-CT findings despite the pathological FIGO stage IA disease.

Estrogen hormone replacement therapy was intentionally postponed until completion of chemotherapy and confirmation of remission, after which it was initiated to induce pubertal development and address the consequences of prolonged estrogen deficiency. Because therapy was initiated only recently, its long-term effects on pubertal development, bone health, and metabolic outcomes remain under evaluation. Throughout her treatment, supportive management included a low-carbohydrate, low-fat diet, calcium and vitamin D supplementation, regular weight-bearing exercise, and targeted management of metabolic risk factors.

Further evaluation of the affected siblings was performed where feasible. The eldest affected brother was unavailable for evaluation because he resides in another city; however, he has fathered two children. The second affected brother (24 years) had tall stature (184 cm) and obesity (123 kg; BMI 36 kg/m²). Left wrist radiography demonstrated persistent open epiphyses, and DXA showed markedly reduced lumbar spine bone mineral density (Z-score −3.0). Laboratory investigations revealed suppressed estradiol <18.4 pmol/L, normal FSH 7.2 IU/L, normal LH 5.3 IU/L, normal testosterone 18.1 nmol/L, and dyslipidemia.

Discussion

Aromatase deficiency is an extremely rare autosomal recessive disorder caused by pathogenic variants in the CYP19A1 gene, resulting in impaired conversion of androgens to estrogens. The consequent estrogen deficiency affects multiple organ systems and leads to abnormalities in sexual development, reproductive function, skeletal maturation, and metabolic homeostasis [1,2]. Although the clinical phenotype is now better recognized, diagnosis remains challenging because of the rarity of the disorder and its overlap with other disorders of sex development, particularly CAH in virilized 46,XX infants. Our patient illustrates these diagnostic challenges, as she remained incorrectly diagnosed with CAH for 16 years before the discordance between her clinical course and biochemical findings prompted reassessment and confirmation of AD by identification of a homozygous pathogenic CYP19A1 variant.

The initial diagnosis of 21OHD was based on ambiguous genitalia at birth and an elevated neonatal 17-OHP concentration. However, transient elevation of neonatal 17- OHP has also been described in AD and does not necessarily establish 21OHD [4]. In retrospect, several clinical features argued against 21OHD, including the absence of adrenal crisis despite poor adherence to glucocorticoid and mineralocorticoid therapy, normal serum electrolytes and blood pressure, normal basal and ACTH-stimulated 17- OHP concentrations, and an adequate cortisol response to ACTH stimulation testing. Reevaluation during transition to adult endocrinology care revealed hypergonadotropic hypogonadism with profoundly reduced estradiol concentrations, findings that redirected the diagnostic workup toward estrogen biosynthesis disorders and ultimately established the diagnosis of AD. This case emphasizes the importance of reconsidering the diagnosis whenever the clinical course is inconsistent with CAH.

An interesting feature in our patient was the absence of clinical signs of hyperandrogenism and the presence of normal circulating testosterone levels. Although AD impairs the conversion of androgens to estrogens, normal serum testosterone levels have been reported in several patients with AD, highlighting the phenotypic variability of this disorder [4,5]. Virilization in affected females primarily reflects excessive androgen exposure during fetal development, whereas circulating androgen levels during adolescence and adulthood may remain within the normal female range.

Estrogen plays a pivotal role in skeletal maturation and bone remodeling. It promotes epiphyseal fusion, suppresses osteoclast-mediated bone resorption, enhances osteoblast survival, and is essential for the acquisition and maintenance of bone mineral density [7,8]. Consequently, prolonged estrogen deficiency results in delayed skeletal maturation and impaired bone health. These features were evident in our patient, who had persistent open epiphyses, markedly delayed bone age, continued linear growth, and severe reduction in lumbar spine bone mineral density. Similar skeletal abnormalities were also observed in her affected brother, despite normal testosterone concentrations, further supporting the concept that estrogen, rather than testosterone alone, is essential for normal skeletal maturation. Estrogen replacement therapy therefore represents the cornerstone of treatment, promoting epiphyseal closure, improving bone mineral density, and reducing long-term fracture risk [8].

Beyond its skeletal effects, estrogen is increasingly recognized as a key regulator of metabolic homeostasis. It influences adipose tissue distribution, enhances insulin sensitivity, and plays an important role in maintaining normal glucose and lipid metabolism. Consequently, prolonged estrogen deficiency predisposes affected individuals to metabolic dysfunction [9,10]. Consistent with this, both our patient and her affected brother developed obesity and adverse metabolic abnormalities, supporting the contribution of estrogen deficiency to their metabolic phenotype. Estrogen replacement therapy has been shown to improve metabolic outcomes in patients with AD [11].

Ovarian morphology in AD is heterogeneous. Most reported female patients demonstrate enlarged multicystic ovaries, which are thought to result from chronic gonadotropin stimulation secondary to prolonged estrogen deficiency [4]. However, hypoplastic or dysplastic ovaries have also been described [12]. The recent single-center experience and systematic review by Yami Channaiah and colleagues confirmed that impaired ovarian development forms part of the phenotypic spectrum of AD [4]. Consistent with this variability, our patient exhibited marked ovarian asymmetry, with a dysplastic left ovary containing microscopic foci of gonadoblastoma and a markedly enlarged right ovary harboring gonadoblastoma with dysgerminoma. Whether this asymmetric ovarian phenotype reflects AD alone or represents a coincidental association remains uncertain.

The Müllerian phenotype in our patient was also unusual. Pelvic MRI demonstrated a markedly hypoplastic uterus and vagina, while surgery identified a markedly hypoplastic uterus but did not visualize the cervix or vaginal canal. These findings were interpreted as severe Müllerian hypoplasia rather than confirmed congenital absence. Although estrogen deficiency may impair Müllerian maturation and pubertal development, the extent to which AD alone accounts for this phenotype remains uncertain. As molecular analysis of the gonadal tissue and assessment for occult Y-chromosome material, including SRY and other Y-specific sequences by FISH or PCR, were not performed, the presence of an additional gonad-specific developmental or somatic genetic abnormality cannot be completely excluded.

To our knowledge, this is the first reported case of genetically confirmed AD with coexisting gonadoblastoma and dysgerminoma. Gonadoblastoma typically develops in dysgenetic gonads containing Y chromosome material; however, rare cases have also been reported in 46,XX individuals without detectable Y chromosome sequences and in association with endocrine disorders such as 17α-hydroxylase/17,20-lyase deficiency and pure gonadal dysgenesis [13-15]. These observations suggest that mechanisms other than Y chromosome material may contribute to tumorigenesis. Chronic gonadotropin stimulation resulting from longstanding estrogen deficiency and persistent gonadal dysfunction may represent one possible mechanism, although further clinical reports and mechanistic studies are required to determine whether the coexistence observed in our patient reflects a true biological relationship or a coincidental finding.

Estrogen replacement therapy remains the cornerstone of management in AD. In females, gradual estrogen replacement promotes pubertal development, uterine growth, and long-term skeletal and metabolic health. When the uterus is present, cyclic progesterone should be introduced after adequate estrogen priming to protect the endometrium. Similarly, affected males also benefit from estrogen replacement, which may improve skeletal, metabolic, and reproductive outcomes [16]. Supportive management should include adequate calcium and vitamin D intake, regular weight-bearing exercise, and monitoring of skeletal and metabolic outcomes. Overall, long-term multidisciplinary follow-up is essential to optimize lifelong management.

Conclusion

Aromatase deficiency may go unrecognized until adolescence or adulthood, particularly when early virilization leads to a presumptive diagnosis of CAH without definitive biochemical or genetic confirmation. Delayed diagnosis postpones estrogen replacement therapy, impairing pubertal development, bone accrual, body composition, and psychosocial well-being. This case documents the first reported co-occurrence of genetically confirmed AD with gonadoblastoma and dysgerminoma. Although no causal relationship can be inferred from a single observation, additional reports are needed to determine whether this coexistence reflects a true biological relationship or a coincidental finding.

Informed Consent

Written informed consent was obtained from the patient for publication of this case report.

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Table 1. Baseline Hormonal and Metabolic Profile of the Patient

Parameter	Result	Reference/ Desirable Range	Interpretation
Na (mmol/L)	140	134-145	Normal
K (mmol/L)	4.5	3.5-5	Normal
Renin (mU/L)	38.7	4-60	Normal
ACTH (ng/L)	31.7	5-60	Normal
FSH (IU/L)	94.4	1.5–12.4	Elevated
LH (mIU/mL)	47.1	1.7–8.6	Elevated
Estradiol (pmol/L)	<18.4	36.7-660	Very Low
Prolactin (pg/mL)	21.4	4.8–23.3	Normal
Testosterone (nmol/L)	0.34	0.3–2.1	Normal
AMH (ng/mL)	3.32	o.77–14.5	Normal
HbA1c	6 %	<5.6 %	Prediabetes range
Cholesterol (mmol/L)	6.2	< 5.2	Elevated
LDL (mmol/L)	4.84	< 2.6 (optimal)	Elevated
HDL (mmol/L)	1.23	> 1.3	Slightly low
Triglyceride (mmol/L)	2.14	< 1.7	Elevated
β-hCG (U/L)	1.9	< 5	Normal
AFP (ug/L)	1.65	0-7	Normal

CA-125 (U/mL)	10.9	<35	Normal
ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; AMH, anti-Müllerian hormone; HbA1c, glycated hemoglobin; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; β-hCG, beta-human chorionic gonadotropin; AFP, alpha-fetoprotein; CA-125, Cancer Antigen 125.			

Table 2. Baseline and Post-ACTH Stimulation Cortisol and 17-Hydroxyprogesterone Levels

Time Point	Cortisol (nmol/L)	17-OHP (nmol/L)
Baseline (0 min)	268	3.2
30 min	527	3.9
60 min	600	4.0
17-OHP; 17-Hydroxyprogesterone		

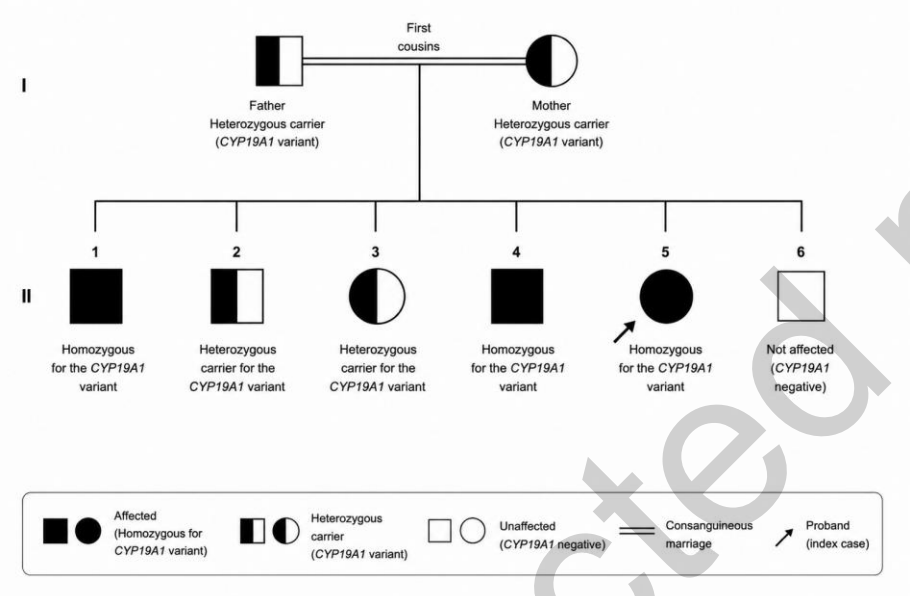

Figure 1. Family pedigree demonstrating autosomal recessive inheritance of a pathogenic CYP19A1 variant in a consanguineous family. Squares represent males and circles represent females. Filled symbols indicate affected homozygous individuals, half-filled symbols indicate heterozygous carriers, and open symbols indicate unaffected individuals. Double horizontal lines denote consanguineous marriage. The proband is indicated by an arrow.

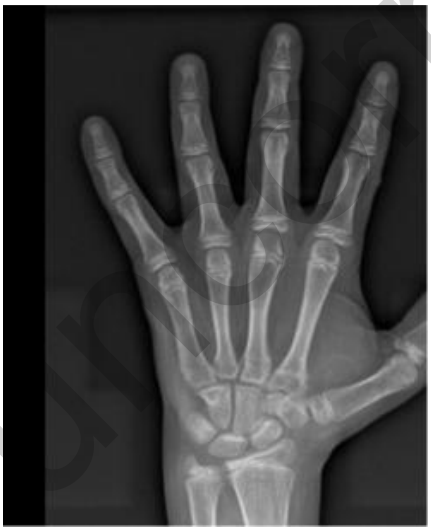

Figure 2. Left hand and wrist radiograph of the index patient for bone age assessment.