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AN XY FEMALE

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ABSTRACT

Background: Primary amenorrhoea (PA) is defined as the lack of menstruation at age 13 years in the absence of normal growth and secondary sexual characteristics, or lack of menstruation at age 15 years in the setting of normal growth and secondary sexual characteristics. Most underlying causes of PA can be classified into gonadal, anatomic, endocrine and systemic causes. Disorders of sexual development (DSD) are a rare, yet challenging aetiology.

Case description: We present a 24-year-old, previously healthy female, who complained of PA and absent breast development. The patient denied any other symptoms. The physical examination revealed a tall girl, with infantile breasts and unambiguous female external genitalia, with no abnormalities. Laboratory tests showed hypogonadotropic hypogonadism (HH), undetectable anti Müllerian hormone (AMH), present Müllerian structures and absent ovaries in the pelvic magnetic resonance imaging (MRI), with a 46,XY karyotype. The abdominal and pelvic laparoscopy confirmed the presence of Müllerian structures, with no evidence of gonadal tissues. A diagnosis of early testicular regression syndrome (ETRS) was given. Hormonal replacement therapy (HRT) was started and escalated thereafter, resulting in regular menses, breast development and patient satisfaction.

Conclusion: PA in a 46,XY female is a challenging disorder. Although several differential diagnoses are considered, the unique clinical, hormonal, radiological and cytogenic findings are helpful in suggesting the diagnosis of ETRS.

KEYWORDS

Primary amenorrhoea, testicular regression syndrome, XY female, gonadal dysgenesis, Swyer syndrome

LEARNING POINTS

- Primary amenorrhoea can be caused by defects at various levels.
- The disorders of sexual development are important, yet less frequent, causes of primary amenorrhoea.
- The successful management of primary amenorrhoea relies on a multidisciplinary approach.

BACKGROUND

Primary amenorrhoea (PA) is a challenging condition that can result from genetic or non-genetic factors, leading to defects in sexual development at various levels. The comprehensive assessment of PA is triggered in the physician's office three years post thelarche, or within five years if breast

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development has started before the age of 10 years[1]. Here, we present a case of PA of a challenging diagnostic process.

CASE DESCRIPTION

A 24-year-old, previously healthy female was referred from the Obs & Gynae Outpatients Department at the age of 16 for PA and lack of breast development. The patient denied symptoms of weight loss, abnormal eating habits, hirsutism, abnormal pigmentation, headache, dizziness, visual disturbances, galactorrhoea, abdominal or pelvic discomfort, genito-urinary symptoms, fractures or hot flushes. She was in high school and distressed for not experiencing menses as her peers. She was not sexually active. Drug and family history was unremarkable.

Physical examination: Blood pressure (BP) was normal with no postural dizziness; height was 168 cm and weight 93 kg. The breasts were prepubertal. The head, neck, abdomen and visual fields examination was unremarkable. Genital examination showed female unambiguous infantile external genitalia and sparse axillary and pubic hair.

The investigations demonstrated HH with undetectable AMH *(Table 1)*. The genetic testing revealed a 46,XY karyotype with positive sex-determining region on the sex-determining region Y (SRY) gene. The left-hand radiograph revealed a bone age of 14 years with an opened epiphysis. The initial pelvis MRI showed present Müllerian structures with an infantile uterus and absent ovaries *(Fig. 1A)*; the findings were confirmed by magnetic resonance angiography (MRA). A pelvic and abdominal laparoscopy revealed present Müllerian structures (a uterus and two fallopian tubes with fimbrial ends) without evident gonadal tissue. The patient was diagnosed with early testicular regression syndrome (ETRS). Puberty was induced by hormonal replacement therapy (HRT) three years later, resulting in satisfactory breast development, sexual hair growth and regular menses. After seven years of presentation, no change in tumour markers' level was detected *(Table 1)*, and no gonadal tissues were identified in follow-up pelvis and abdominal MRI and MRA studies, but uterus growth was noticed *(Fig. 1B and 2)*. The epiphysis was fully fused with a bone age above 18 years.

Index	Initial results	Follow-up result	Reference range
Haemoglobin (g/l)	135	13.1	120–150
Glucose (mmol/l)	6.1	5	4.1–6
Sodium (mmol/l)	139	138	136–146
Potassium (mmol/l)	5.05	4.57	3.5–5.1
Alkaline phosphate (IU/l)	124	50	47–119
Gamma-glutamyl transferase (IU/l)	31	18	4–24
Alanine aminotransferase (IU/l)	18	10	2–35
Aspartate aminotransferase (IU/l)	23	19	1–35
Total cholesterol (mmol/l)	-	4.62	<4.4 (≤18 years old) <5.2 (≥19 years old)
Low-density lipoprotein (mmol/l)	-	2.63	<2.59
Triglycerides (mmol/l)	-	0.6	<0.85 (≤19 years old) <1.3 (20-24 years old)
Oestradiol (pmol/l)	104	135	88–419
Luteinising hormone (IU/l)	14.2	15.9	2.12–10.89
Follicle-stimulating hormone (IU/l)	56.6	37	0.3–10
Prolactin (mIU)	195	196	95–572
Anti-Müllerian hormone (ng/ml)	0.01	0.001	<0.3: very low
Alpha-fetoprotein (IU/ml)	1.67	<1.1	0–10
Cancer antigen 125 (IU/ml)	20.3	11.63	0–35
Beta-human chorionic gonadotropin (mIU/ml)	<0.6	0.55	>5: pregnant
Lactate dehydrogenase (IU/l)		134	125–247

Table 1. The initial and follow-up blood, biochemical, hormonal and tumour markers investigations.

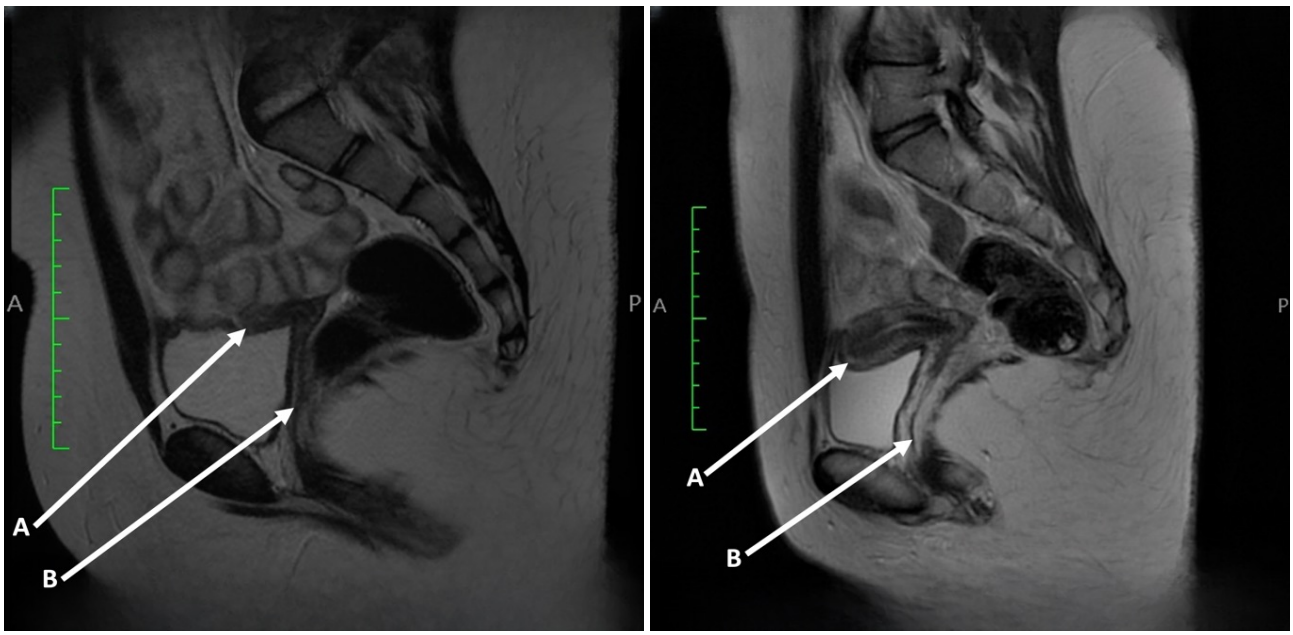


Figure 1. Sagittal T2 image of the uterus: pre-treatment MRI measuring 0.98 × 2.8 × 1.5 cm (AP × CC × TR) and volume 2.16 cc with no gonadal tissues detected on the left, and post-treatment measuring 2.35 × 5.7 × 3.1 cm (AP × CC × TR) with volume 21.7cc, demonstrating a time-interval increase in the size of the uterus on the right. A) uterus and B) vagina.

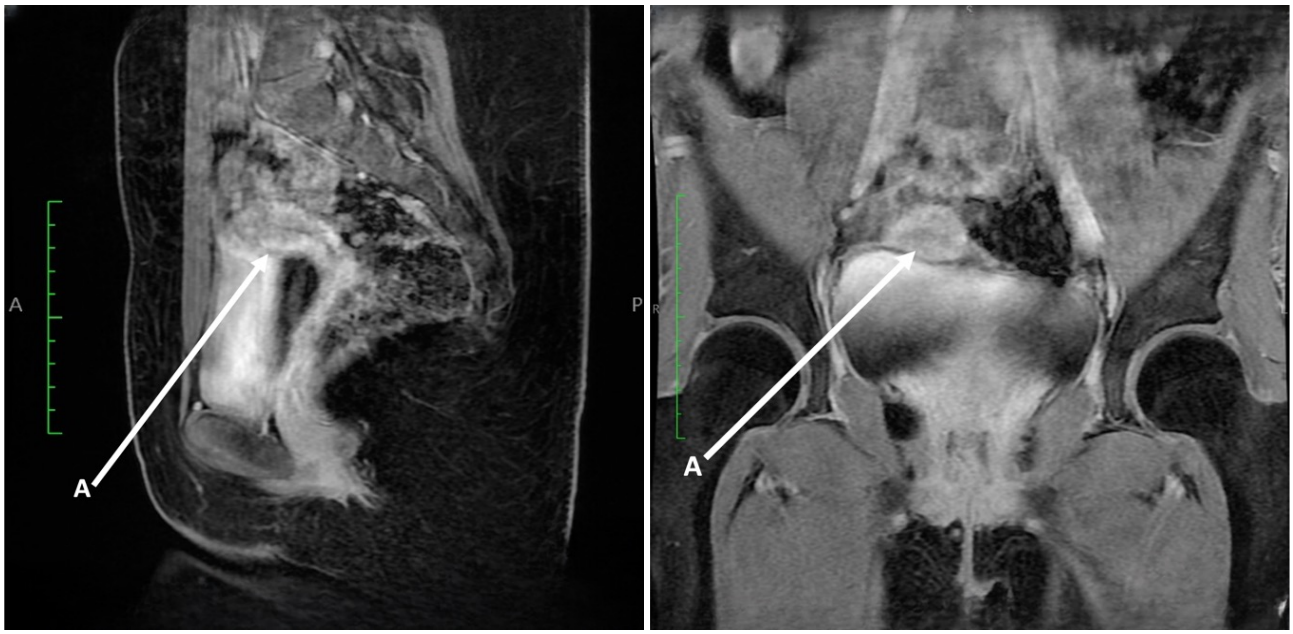


Figure 2. On the left, sagittal post-contrast T1 with fat saturation images of MRA post-treatment that showed the absence of any gonadal tissue or gonadal vessels. On the right, coronal post-contrast T1 with fat saturation images of MRA post-treatment that showed the absence of any gonadal tissue or gonadal vessels. A) normally enhancing uterus.

The DEXA scan showed normal bone mineral density with a Z-score within the expected range for age. Most recently the patient looked satisfied, with a height of 172.5 cm, weight of 80 kg, BMI of 26.9 BP 126/77 mm/Hg and breast Tanner Stage 5 with normal axillary hair.

DISCUSSION

Hypogonadotropic hypogonadism can be caused by functional defects at gonadal, enzymatic, hormonal or receptor levels. This case was challenging as the patient demonstrated karyotype-phenotype mismatch, representing a case of disorders of sexual development (DSD), and manifesting the difficulties in differentiating these similar conditions. 29.6% of PA cases lack breast development[2], HH occurs in 29%[3], and male karyotype accounts for only 3.4%[2].

Sex is determined in the embryonic bipotential gonads by transcriptional regulation. Ovarian differentiation is the default pathway unless a normal SRY gene triggers testis development. By the eighth gestational week, hormonal regulation directs the Müllerian or Wolffian duct differentiation. AMH induces Müllerian duct regression, while testosterone differentiates Wolffian ducts and virilises the external male genitalia[4]. Gonadal causes of underutilised

Condition	Defect level	Breast development	Internal genitalia	Gonads
Embryonic testicular regression syndrome	Gonadal	No	Müllerian	None
True ovarian agenesis	Gonadal	No	Müllerian	None
Pure gonadal dysgenesis (Swyer syndrome)	Gonadal	No	Müllerian	Streak
Androgen insensitivity syndrome	Receptor	Yes	None	Testes
Leydig cell hypoplasia	Hormonal	No	Blind vagina, Wolffian structures	Testes
17-α hydroxylase/17,20-lyase deficiency	Enzymatic	No	Blind vagina, Absent Müllerian structures	Testes
5-reductase deficiency	Enzymatic	No	Blind shallow vagina, Wolffian structures	Testes

Table 2. The differential diagnoses of a 46 XY female and their major discriminatory features.

46,XY foetuses constitute 40.1% of the cases[5]. Only 2% of the cases retain a uterus with a male karyotype[2] *(Table 2)*.

Testicular regression syndrome (TRS) results from a lack of testicular formation or maintenance during gestation[4]. The timing of testicular regression is critical. If testicular regression occurs early in foetal sex development, males will lack virilisation with the retaining of female internal genitalia. Laparoscopy assists in the localisation of the non-palpable testis, with a success rate of 90–95%[6].

There are few reports of ETRS resulting in female external genitalia with rudimentary Müllerian structures[4]. Although TRS is sporadic, there are familial reports that might be associated with other defects[6]. Y-chromosome rearrangement and DMRT1 repression might be implicated[7]. In this case, further genetic testing for possible mutations was not feasible in our service. TRS theoretically carries a potential for malignant degeneration in the long term[5]. As minimal gonadal tissues could not be ruled out, sequential pelvic and abdominal MRIs were performed and confirmed a lack of growing gonadal tissues post HRT, supporting ETRS diagnosis.

True ovarian agenesis (gonadal agenesis) was described in 1944. The patients present with PA, lack of gonads and secondary sexual characteristics with female gender identity and internal differentiation. The karyotype is 46,XX or 46,XY[8].

Pure gonadal dysgenesis is a rare disorder that is caused by a mutation in the SRY gene or other downstream genes, and results in a phenotypic female with Müllerian structures and streak gonads. The presence of the Y-chromosome increases gonadal malignancy potential[8]; the lack of gonadal tissues in our case made this possibility less likely.

Both 46,XY gonadal dysgenesis and TRS are considered as a continuum of testicular errors in testis development, rather than clearly distinct categories. Both conditions may share a common genetic aetiology including variation in the DEAH-box RNA helicase DHX37[6,9].

Androgen insensitivity syndrome is caused by a mutation of the androgen receptor gene on the X chromosome. It is the third most common cause of PA after gonadal dysgenesis and congenital absence of the vagina. In the complete form, unequivocally female presents with inguinal hernia or PA. The sexual hair is diminished or even absent while the breast development and body fat are female[10]. The testicles may be ectopic and neither Wolffian nor Müllerian structures develop, but the vagina is short and blind. Receptor-positive resistance was documented in one family[10]. In our patient, the lack of breast development and the presence of uterus and pubertal hair growth makes this diagnosis less likely. Other DSDs were excluded *(Table 2)*.

CONCLUSION

This case illustrates the complexity of sexual development. ETRS could be suspected in an XY female with present Müllerian structures and absent gonads. The management should be approached by a multidisciplinary team considering other differential diagnoses.

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