

46, XY Female—A Case Report

M K S Leow,*^{MBBS, M Med (Int Med)}, K C Loh,**^{FAMS, FACP, FRCPE}

Abstract

Introduction: We examine a presumptive case of complete androgen insensitivity syndrome (CAIS) with certain unusual features. **Clinical Picture:** A woman with early onset osteoporosis gave a history of primary amenorrhoea and surgery for intraabdominal gonads. She subsequently defaulted follow-up and hormone replacement therapy. Endocrinological evaluation revealed hypergonadotrophic hypogonadism associated with a 46,XY karyotype. **Treatment:** Therapy included reinforcement of the female phenotype and oestrogen replacement. **Outcome:** There was gradual development of her secondary sexual characteristics and improvement in her bone mineral density. **Conclusion:** Patients with CAIS need proper counselling and education according to their psychosexual make-up and sociocultural factors. The importance of long-term oestrogen replacement in a young subject post-gonadectomy cannot be overemphasised as illustrated in our case.

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Key words: Androgen insensitivity syndrome, Atypical presentation, Male pseudohermaphroditism, Management, Testicular feminisation syndrome

Introduction

The phenotypic sex of an individual is usually male if that person's genotype is 46, XY since the SRY gene on the Y chromosome, being the putative testicular determining factor (TDF)¹ governs testicular gonadogenesis. Yet, there are distinct situations where sexual differentiation proceeds along a female phenotype despite the presence of the Y chromosome. This article looks at a presumptive case of complete androgen insensitivity syndrome and examines some unusual features unique to this patient and their impact on clinical management.

Case Report

A 40-year-old unmarried woman with a compression fracture of the second lumbar vertebra following a trivial fall was assessed at our osteoporosis clinic (Fig. 1). She had a past history of bronchial asthma during her childhood, but had never used any corticosteroids. Apart from being sedentary and consuming little dairy products, she had no other risk factors for osteoporosis. Interestingly, however, she had a history of primary amenorrhoea and she was evaluated at a women's hospital at age 16 whereby her gonads were apparently removed. Unfortunately, both her parents were unaware of the diagnosis then, and neither did

they fully understand the significance of the surgery nor the necessity for life-long hormone replacement therapy (HRT). As such, though she was initiated on hormone replacement postoperatively, she defaulted after a few months. Her birth history was unremarkable and there was no developmental milestones delay. However, she had delayed development of secondary sexual characteristics. She is the fourth child in a family of seven children, and she was apparently the tallest among her 5 sisters, all of whom have normal menstrual cycles.

Clinically, the patient was 161 cm tall and had normal body proportions. She was normotensive. There was complete absence of axillary and pubic hair, and her breast development was Tanner stage 2 with mammary glandular tissue measuring 3 cm bilaterally. Abdominal examination revealed a low transverse abdominal laparotomy scar. She had infantile female external genitalia with no evidence of virilisation. A vaginal examination was not performed, but an abdominopelvic ultrasound showed the absence of uterus and ovaries. Biochemical tests revealed normal serum urea, electrolytes, calcium and phosphate. Hormonal investigations showed a serum follicle-stimulating hormone (FSH) level of 141 U/L, serum luteinizing hormone (LH) level of 44.7 U/L with an oestradiol level of 36.7 pmol/L.

* Registrar in Endocrinology

** Consultant Physician and Endocrinologist
Endocrine Unit

Department of General Medicine
Tan Tock Seng Hospital

Address for Reprints: Dr Melvin Leow Khee Shing, Department of Medicine, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433.

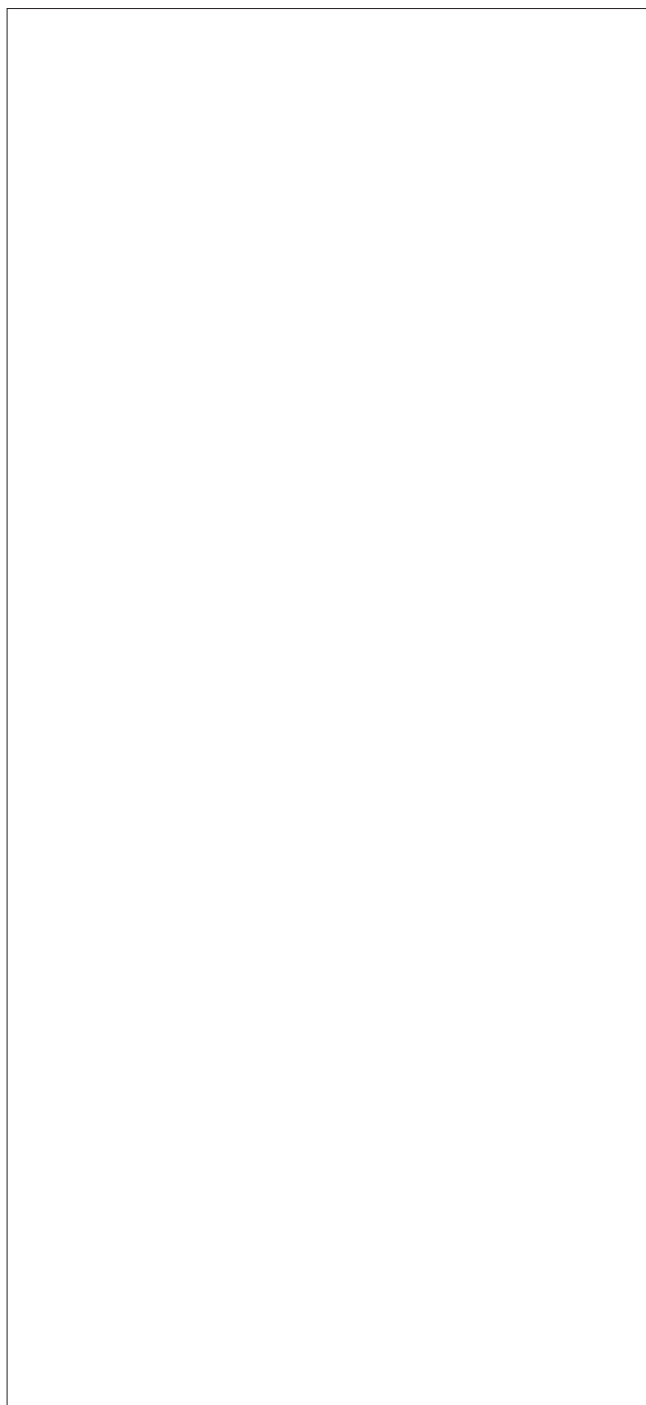


Fig. 1. Roentgenogram of lumbosacral spine (lateral view) showing compression fracture of the second lumbar vertebra and pronounced osteopaenia.

Serum testosterone level was undetectable. Serum dehydroepiandrosterone level was 3.1 $\mu\text{mol/L}$. Basal serum cortisol was 206 nmol/L, progesterone was 0.8 nmol/L and 17 α -OH progesterone was 1.1 nmol/L. Following a short adrenocorticotrophic hormone (ACTH) stimulation test (IV Synacthen 250 μg), serum cortisol and 17 α -OH progesterone levels rose to 770 nmol/L and 6.0 nmol/L respectively at 30 minutes. Thyroid function results were

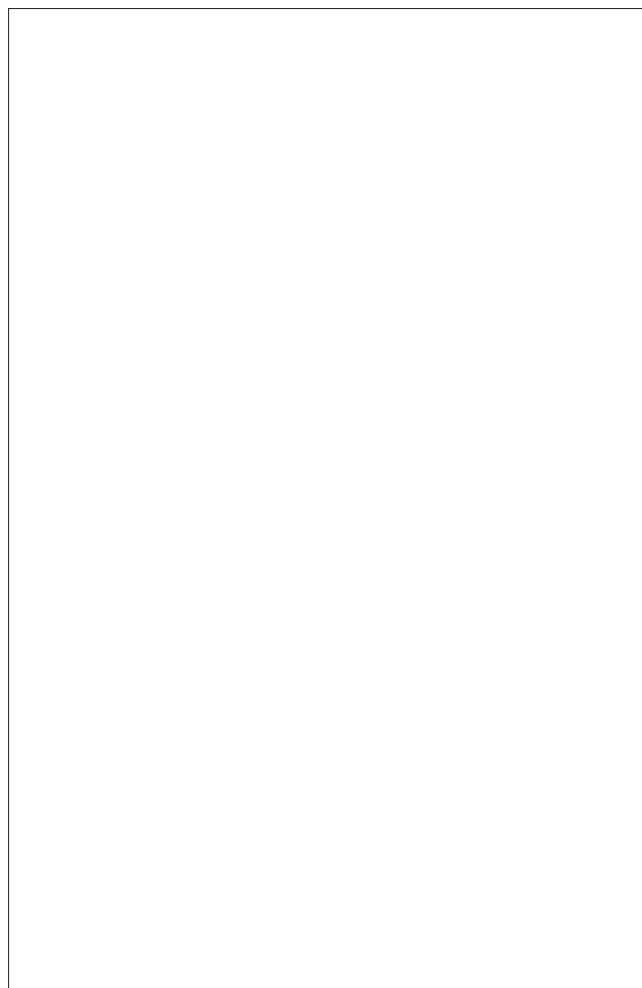


Fig. 2a. Bone mineral density analysis of left neck of femur.

normal. Chromosomal analysis revealed a normal male karyotype (46, XY). Bone mineral densitometry (BMD) using a dual energy X-ray absorptio-metry scanner (Hologic 2000) confirmed osteoporosis with T-score of -2.59 at the left femoral neck corresponding to a BMD of 0.487 g/cm² (Fig. 2a), and -3.54 at the 3rd to 4th lumbar vertebrae (anterior-posterior) corresponding to a BMD of 0.607 g/cm² (Fig. 2b).

She was counselled on her condition and started on oestrogen replacement therapy with premarin. Calcium and vitamin D supplements were also prescribed. When she was reviewed 3 months later, there was some increase in breast size. Her backache had completely resolved.

Discussion

In individuals with 46, XY karyotype but yet manifest the female phenotype, the pathogenetic mechanisms can be classified into 2 main groups as shown in Table I. Excluding the transsexual male who has undergone sex reassignment operation, the above list of differential diagnosis constitutes

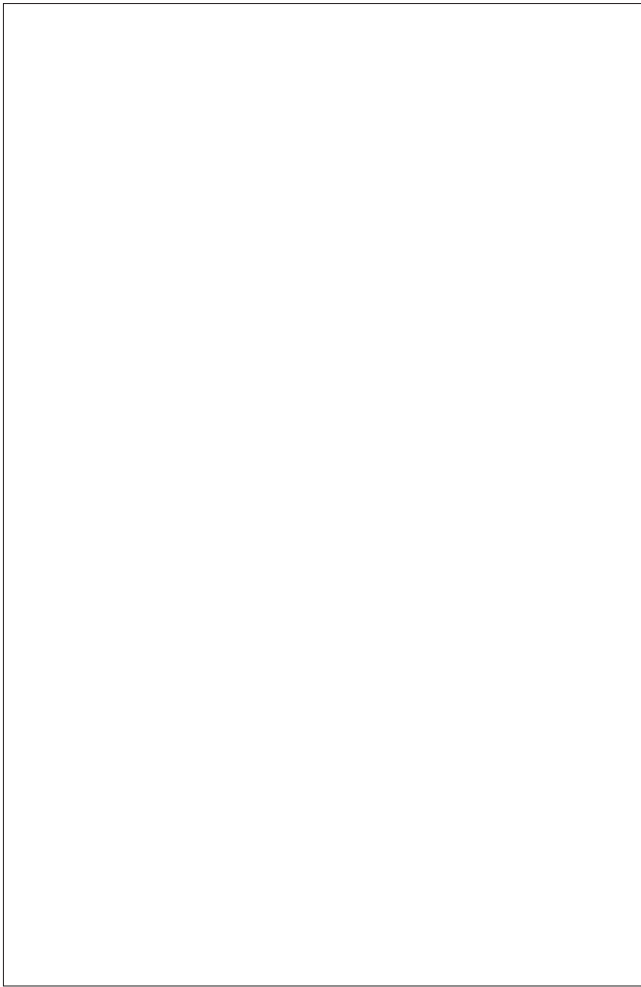


Fig. 2b. Bone mineral density analysis of lumbar spine (anterior-posterior).

TABLE I: DIFFERENTIAL DIAGNOSIS OF 46, XY FEMALES

A	46, XY gonadal dysgenesis
	(i) mutations/deletions of SRY gene ²
	(ii) duplication of dosage-sensitive sex reversal (DSS) locus on the X chromosome (Xp21-p22) ³
	(iii) deletions of distal 9p chromosome (9p23.3-p24.1) ⁴
	(iv) deletions of the distal 10q chromosome (10q26-qter) ⁵
B	(v) mutations of SRY-like high mobility group box (SOX9) gene (17q24.3-q25.1) ⁶
	Male pseudohermaphroditism
	(i) testicular resistance to human chorionic gonadotrophin (HCG) and luteinizing hormone (LH) ⁷
	(ii) enzymatic defects in testosterone biosynthesis
	(iii) end-organ resistance to androgens
	(iv) dysgenetic male pseudohermaphroditism

an effective framework upon which we can analyse a phenotypically female subject with a male genetic sex. As a whole, XY gonadal dysgenesis is rare. Patients with the complete form of 46, XY gonadal dysgenesis (Swyer's syndrome) have female external genitalia, normal or tall stature, bilateral streak gonads, mullerian duct development,

sexual infantilism and eunuchoid habitus. Primary gonadal failure is reflected by elevated plasma LH and FSH associated with a low plasma oestradiol concentration. Pelvic ultrasound reveals a small uterus, but ovaries are frequently absent. Our patient is unlikely to have this entity because she has normal body proportions and she lacks a uterus, although we could not exclude the possibility of surgical removal and have not done cytogenetic studies beyond karyotyping.

Male pseudohermaphroditism, on the other hand, is by far much commoner. This is a heterogeneous group of disorders in which the gonads are exclusively testes but the genital ducts or external genitalia or both exhibit the female phenotype or an incompletely differentiated male. Male development does not take place in these individuals because of failure of the foetal testes to suppress the inherent pathway toward feminisation of the foetus. This may arise from secretory defect of the testes during the critical period of sex differentiation or it may result from resistance of the target tissue to androgen. Importantly, male differentiation of the external genitalia and urogenital sinus is highly dependent on androgens between the 8 to 12 weeks of embryogenesis. Beyond this critical period, after the separation of the vagina from the urogenital sinus, masculinisation cannot occur despite an intense androgenic stimulus. These patients are phenotypically female and show heterosexual orientation.

Among the various causes of male pseudohermaphroditism, complete androgen insensitivity syndrome (CAIS) or testicular feminisation syndrome best explains her condition. However, it is noteworthy that the clinical features in our patient have been influenced by surgical castration carried out during early puberty and inadequate oestrogen replacement subsequently. CAIS is an X-linked recessive disorder with prevalence estimated at 1 in 20,000 male live births.⁸ Classically, these patients have unambiguous female external genitalia and their testes are variably located in the labia majora, inguinal canal or the abdomen. Testosterone and anti-mullerian hormone synthesis are intact and hence, mullerian derivatives are absent. During infancy or childhood, the condition may be suspected when these "girls" present with bilateral inguinal herniae containing testes. However, they usually present during adolescence because of primary amenorrhoea as in this patient. Their pubic and axillary hair is typically sparse or completely absent because of androgen resistance, another feature noted in our patient. Women with CAIS may be relatively tall and they have heterosexual orientation. Typical hormonal profile includes normal or elevated testosterone levels, high serum LH at puberty and serum oestradiol level between normal male and female ranges. Concentrations of adrenal androgens including

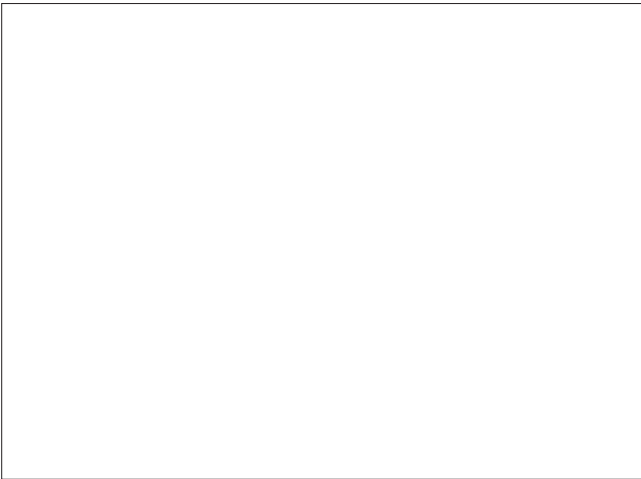


Fig. 3. Molecular organisation of the androgen receptor, from the level of the gene to the translated protein product, showing its 3 domains.

DHEA are normal, thus excluding the diagnosis of congenital adrenal hyperplasia. Histologically, their testes show Leydig cell hyperplasia with tendency toward adenomatous changes and they are predisposed to malignant transformation particularly in the presence of elevated gonadotrophin levels post-pubertally. The risk of testicular neoplasm in affected adults is approximately 4% to 9%,⁹ though this appears to be significantly less in those under 20 years of age.

Significant strides have been made in the understanding of the pathogenesis of this disorder. The underlying pathophysiology of CAIS lies at the level of the androgen receptor (AR) which is encoded by the 90 kilobase androgen receptor gene spanning 8 exons at Xq11-12.¹⁰ Two groups of patients with CAIS have been described—those with absent dihydrotestosterone (DHT) binding and those with normal cytosolic and nuclear binding, but with qualitative abnormalities in ligand-receptor binding kinetics. The human AR belongs to the nuclear receptor superfamily of transcription factors and is structurally and functionally related to the retinoid-steroid-thyroid nuclear receptors. It has 3 major domains, chiefly the androgen-binding region, a DNA-binding region and a transactivating amino-terminal domain (Fig. 3).¹¹ During the ligand-free state, the androgen-binding site is associated with chaperone heat-shock proteins which inhibit DNA binding. Binding of androgens to the steroid-binding site induces a conformational change in the receptor, phosphorylation, dimerization, nuclear translocation and gene transactivation. Impaired androgen-induced transactivation leads to the state of androgen insensitivity. To date, an extremely large number of molecular lesions have been documented based on DNA analysis of the AR gene.¹² Our patient is likely to have a sporadic mutation of the AR gene since all her sisters have normal reproductive function.

Our patient poses a diagnostic challenge because of her past history of gonadectomy. Unlike the classical patient who have well-endowed female secondary sexual characteristics, her breasts are under-developed because of gonadectomy and her subsequent default from HRT. However, her relatively tall stature and complete absence of secondary sexual hair support the diagnosis of CAIS. Similarly, her testosterone level was undetectable because of gonadectomy. Yet her serum oestradiol level is relatively elevated like a genetic male. Serum FSH and LH are usually elevated in such individuals, though gonadectomy will further elevate the gonadotrophins into the menopausal range as seen in this patient. Thus, CAIS with such atypical features may be difficult to diagnose without confirmatory genetic testing. Molecular confirmation of CAIS was not performed because this test is not readily available and the patient was not willing to be tested as she was concerned that it could be costly and yet not make any difference to her management.

The principles of management of CAIS remain controversial as the diagnosis is often made after the onset of puberty. The adult patient (i.e. diagnosis made later in life) should be told of her condition and its consequences on fertility only if she is judged to be able to accept the diagnosis well. That their infertility is not amenable to any treatment also requires a clear explanation. As such information can potentially evoke significant emotional mental distress in the patient; it may be best withheld if the subject is deemed to be emotionally unstable or immature. As our patient is an intelligent, mature and educated adult, a detailed explanation into the nature of the disorder was given in such a way that she could understand and accept. An important component of supportive counselling includes the affirmation and reinforcement of the female phenotype and gender identity.¹³ As sexual identity is generally established by 2 to 3 years of age, most of these patients do not find their psychological sex a conflicting issue.¹⁴ It is important that the patient (or the parents if castration was performed at an early age as in our case) should be made to understand the consequences of castration and the need for long-term HRT to avoid sequelae such as osteoporosis and retarded secondary sexual characteristics development as occurred in our patient. Organisations devoted to the support and education of both patients and parents have been formed which offer great help in sorting out such issues commonly encountered.¹⁵ As the risk of testicular cancer before puberty is reportedly negligible in CAIS, orchidectomy is best deferred till late adolescence to allow the patient to undergo spontaneous feminisation at puberty.⁹ The status of the testes may be monitored by pelvic ultrasound or magnetic resonance imaging in those individuals who opted for delayed gonadectomy. Testicular biopsy post-pubertally may be advocated in selected cases

to ascertain the presence of carcinoma-in-situ if gonadectomy is not contemplated during this phase.

In conclusion, CAIS is a relatively common cause of male pseudohermaphroditism and its diagnosis is usually possible without sophisticated molecular biology techniques. Nonetheless, the clinician should be aware of the 'atypical' manifestation as encountered in our patient. The parents should be counselled appropriately and given adequate understanding of its natural history and potential impact on marriage and fertility. This information may be disclosed gradually to the patient herself when she is old enough to comprehend. Of note, they should understand the reason for gonadectomy and its attendant consequences if HRT is not followed faithfully. Reinforcement of the female phenotype and gender identity is crucial and cannot be overemphasised.

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