Primary infertility in a phenotypic male with 46XX chromosomal constitution

T.T. Tan and B.A.K. Khalid

Department of Medicine, Universiti Kebangsaan Malaysia, Jalan Raja Muda, 50300 Kuala Lumpur, Malaysia

Summary: The case of a 32 year old male with normal male adrenarchal hair pattern, bilateral gynaecomastia, a small phallus, hypospadias and bilateral poorly developed testes presenting with primary infertility secondary to azoospermia and a pelvic cyst is described. Repeated chromosomal analysis showed 46XX chromosomal constitution. Laparotomy revealed a simple cyst between the urinary bladder and the rectum.

XX male syndrome is a rare cause of male infertility. The majority of cases is due to interchange of a fragment of the short arm of the Y chromosome containing the region that encodes the testes determining factor with the X chromosome. The presence of a simple cyst in the anatomical location of the uterus to our knowledge has not been reported in the literature.

Introduction

The XX male syndrome was first reported in 1964.¹ It is one of the rarer causes of ambiguous external genitalia and primary infertility in phenotypic males.² The incidence of XX male syndrome is approximately 1 in 20,000 male births.³ Its relative rarity coupled with normal phenotype and normal external male genitalia in some patients with the syndrome often leads to failure of consideration of the condition in the differential diagnosis of a phenotypic male with primary infertility. We describe here an infertile XX male with normal male phenotype and a pelvic cyst situated in the anatomical position of the uterus. The latter to our knowledge has not been reported in patients with XX male syndrome.

Case report

A 32 year old Indian man was referred to our Endocrine Clinic by a consultant urologist for the problem of primary infertility. At the time of presentation he had been married for 4 years and had sexual intercourse 2–3 times per week with failure of ejaculation despite achieving orgasm.

He could not relate his birth history nor about the pregnancy. His childhood history was uneventful. During puberty, however, he developed bi-

lateral gynaecomastia which had persisted ever since. He also noted that his genitalia were rather small. There was no history of mumps or injury to the testicles. He perceived himself as male and there was no ambiguity with gender identity.

Examination showed a 5 foot 8 inches tall muscular man with arm span equal to height. His voice was masculine. He had a male pattern of hair-line distribution, a moustache and beard, and normal axillary and pubic hair (Figure 1). The bilateral gynaecomastia was Tanner's stage 4 (Figure 2). His penile length was 2 cm (flaccid) and hypospadias was noted (Figure 3). The scrotum

Figure 1 Moustache and beard in the patient with 46XX chromosomes.

Correspondence: T.T. Tan, M.R.C.P.(UK).

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Figure 2 The patient with bilateral gynecomastia.

Figure 3 Micropenis, bilateral small testes and the repaired hypospadias.

was bifid and both the testes measured 1 ml in volume and were firm in consistency. The prostate was not felt per rectum. His blood pressure was 140/90 mmHg. Systemic examination was unremarkable.

Investigations revealed serum urea of 3.5 mmol/l, sodium 140 mmol/l and potassium 3.9 mmol/l. Serum cortisol was 498 nmol/l (normal range (NR) 214–497), serum 17 α -hydroxyprogesterone 9.8 nmol/l (NR < 21 nmol/l), urinary pregnanetriol 4.3 μ mol/24 hours (NR 1.2–8.3) and serum dehydroepiandrosterone sulphate 3.2 μ mol/l (NR 2.5–11.1). Serum testosterone was 9.4 nmol/l (NR 12–34), whilst serum follicle stimulating hormone and luteinizing hormone were 21.0 IU/l (NR 1.1–5.9) and 34.4 IU/l (NR 2.6–11.1), respectively. Plasma oestradiol was less than 25 pg/l. Due to absence of ejaculate semen analysis could not be performed. Buccal smears were Barr body positive and sex chromatin count was 22%. Repeated chromosome analysis showed 2n = 46, XX karyotype.

Micturating urethrocytogram showed male type of urethra and the bladder was normal. Ultrasonography of the pelvis showed an ovoid fluid-filled structure measuring about 6.5 cm in diameter posterior to the urinary bladder and indenting its posterior wall (Figure 4). Normal ovarian or uterine structures were not identified and the kidneys were normal.

Exploratory laparotomy was performed and the findings were that of a pelvic cyst, 6 $\times$ 5 cm, lying between the bladder and the rectum (this would be where a uterus would be situated). However, the cyst was filled with clear fluid and the cyst wall was thin (about 3 mm) and smooth, looking more like a duplicate bladder! There was no evidence of uterus, fallopian tubes or ovaries. The cyst did not communicate with the urethra. Histopathological examination of the pelvic cyst showed the lining epithelium of the cyst was squamous in nature, the wall was fibromuscular and there was presence of subepithelial fibrous tissue. No features of malignancy were noted (Figure 5). The impression was that of a simple cyst.

Figure 4 Ultrasonogram of the pelvic cyst lying posteriorly and indenting the posterior wall of the urinary bladder.

Figure 5 Histology of the pelvic cyst showing squamous epithelial lining, subepithelial fibrous tissue and fibromuscular wall ($\times$ 4).

The patient was treated with testosterone for improvement of libido and maintenance of his secondary sexual characteristics. He was counselled on the prospect of reproduction. Psychiatric referral was unnecessary as he had no ambiguity with psychosexual orientation or social maladjustment due to the gynaecomastia.

Discussion

The findings of normal serum cortisol, serum electrolytes and female chromosomal constitution exclude the diagnosis of partial congenital adrenal hyperplasia. Klinefelter's syndrome was unlikely because the arm span of the patient equalled his height and the Y chromosome was not identified. Male pseudohermaphroditism due to partial deficiency of 3β -hydroxysteroid dehydrogenase or partial androgen resistance (Reifenstein syndrome) were also improbable in the presence of 46XX karyotype. Prior to the exploratory laparotomy, the working diagnosis was that of true hermaphroditism as 60% of the latter are of 46XX karyotype,⁴ and malignant transformation of an intrabdominal ovotestes or ovary was seriously considered to be the cause of the pelvic abnormality detected on ultrasonography. The latter was found to be just a

simple cyst and no female internal genitalia were noted.

The clinical features of XX male syndrome most frequently described in the literature are azoospermia, abnormal external male genitalia, normal male adrenarchal hair pattern, normal intelligence, short stature and gynaecomastia.⁵ In a literature review of 90 case reports of XX males, none described the presence of a pelvic cyst at the anatomical location of the uterus.⁶ The pelvic cyst found in our patient could possibly have originated from a remnant of incompletely regressed Mullerian duct.

Most cases of XX male result from the translocation of the testes determining factor gene from the short arm of the Y chromosome to the short arm of the X chromosome.⁷⁻¹¹ All XX males are expected to be azoospermic, since these patients do not possess the long arm of the Y chromosome that contains the azoospermia factor-3 gene which is necessary for normal spermatogenesis.¹²

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