



Case Report

# Red herring: Undervirilisation of male foetus due to maternal oestrogen-producing tumour or an intrinsic problem?

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## ABSTRACT

Disorders of sexual differentiation (DSD) are a cause for significant anxiety. A structured and rapid investigation strategy gives the family solace and the opportunity to institute appropriate therapy. We describe a 46XY undervirilised DSD that was attributed to an estrogen-secreting maternal ovarian cystadenoma tumour. However, diligent and complete workup revealed a different diagnosis altogether. Conservative therapy to support this preterm neonate was first followed; confirmation of the diagnosis helped institute an endocrine consult, anticipatory guidance and regular follow up. Initially apparent causes of DSD must not hamper a detailed algorithmic approach toward a definitive diagnosis.

**Keywords:** Ambiguous genitalia, Androgen insensitivity, Disorders of sexual differentiation, 46XY DSD

## INTRODUCTION

“Boy or girl?” The distress faced by a family who is taken aback by the birth of a baby with disorder of sexual differentiation (DSD) is unimaginable. The medical team is at peril too; managing associated medical emergencies/anomalies, stabilisation of vitals, fluid electrolyte balance, counselling and reassuring the families, are only part of the challenges faced. Delaying gender assignment till some degree of clarity is obtained requires interdisciplinary involvement, and coordination of birth registration processes. An algorithmic approach prevents uncertainty and miscommunications. Overall incidence of DSD has been estimated to be approximately 1 in 4,500-5,500 and that of 46, XY DSD has been estimated to be 1 in 20,000 births.<sup>[1]</sup> Maternal hyperandrogenic states are known to be one of the causes for virilisation of female foetuses.<sup>[2]</sup> We present a case of a 46XY undervirilised preterm neonate born to a mother with ovarian mucinous cystadenoma. We initially attributed the cause to transient hyperoestrogenic state. Clinical features were correlating, and the genital morphology improved on follow-up too. But eventually the revelation came from a genetic diagnosis of Partial Androgen Insensitivity syndrome. This underlines the importance of a complete work up and follow up, even if there appears to be a strong contestant diagnosis.

## CASE REPORT

Mrs AAA, 34 years of age, had gestational diabetes that required insulin therapy. The only other “drugs” she was using were folate, aspirin during first trimester, iron and calcium thereafter. At 32 weeks, she was referred to our centre for acute abdomen diagnosed to be due to ovarian torsion. She underwent open ovariectomy, histopathological examination confirmed mucinous

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cystadenoma of size 11×4×7 cm in left ovary. Since the tumour was removed on an emergency basis, maternal oestrogen levels were not done pre-operatively.

The baby was delivered due to preterm onset of labour by Caesarian section at 32 weeks, and birth weight 2.01 kg. The infant was noted to have features of DSD: stretched phallus length 1 cm, single urogenital opening, right genital fold comparatively prominent with a gonad palpable, left fold was underdeveloped with no palpable gonads [Figure 1]. There were no features of hyperpigmentation, facial dysmorphism or associated urinary tract malformations.

### Management and outcome

The neonate was worked up. Testosterone (T)(4.21 ng/ml), and antimullerian hormone (AMH) (>23 ng/ml) measured in baby's serum on day 1 corresponded to those expected in a normally functioning male gonad. Serum Luteinising hormone was suppressed to 0.1 microIU/ml. Electrolytes,

serum cortisol, sugars, 17-hydroxy progesterone were normal. Ultrasound of the perineum was suggestive of a testicle in the right gonadal fold, left was located in the deep inguinal ring. No Mullerian structures were seen. The clinical team suspected the maternal tumour to be the cause for the undervirilisation of a chromosomal male. Hence, oestrogen (E2) levels were measured in the baby. These were very high at 128.36 pg/ml when tested on day 3 of life. The Fluorescent in situ hybridisation (FISH) tested positive for presence of Y chromosome.

By day 15 of life, left sided gonad was also palpable in inguinal canal, scrotal pigmentation and rugosity increased, phallic length increased to 2 cm. Corresponding oestrogen levels had dropped to 39.84 pg/ml. On Day 23 of life, based on all the above and a confirmed 46XY Karyotype report, baby was assigned male gender by paediatric endocrinologist and discharged home. At one month of age (36 weeks), the baby was gaining weight, stretched penile length was 2.5 cm,



**Figure 1:** (a) Small phallus, left genital fold under-developed with no gonads palpable, (b) Single urogenital sinus, (c) On follow up, bilateral increased rugosity and pigmentation of genital folds (scrotum) and increased phallic length. Right testes descended into better developed scrotum.

bilateral testes descended, scrotum well developed but bifid [Figure 1]. Serum T and DHT were 2.06 ng/ml and 421 pg/ml respectively. The infant was under follow up with Paediatric endocrinology and surgery. The genetic test which was sent as part of the diagnostic algorithm was later reported as a pathogenic variant for partial androgen insensitivity syndrome: hemizygous missense variation in exon 7 of the AR gene (chrX:g.67722838G>C; Depth: 112x) that results in the amino acid substitution of Arginine for Glycine at codon 821 (p.Gly821Arg; ENST00000374690.9).

## DISCUSSION

We describe a case where maternal female sex hormones in excess, probably from very early in the first trimester was considered to be the cause for severe undervirilisation of a male foetus. The need for continued evaluation is emphasized by this report as the final diagnosis was an intrinsic genetic disorder.

The incidence of ovarian tumours complicating pregnancy ranges between 1% and 2%. Authors have described female fetal virilisation by maternal thecomas, malignant Sertoli-Leydig tumours and pregnancy luteomas.<sup>[2]</sup> To the best of our knowledge, our report would be a unique account of a mucinous cystadenoma associated with the birth of an undervirilised XY DSD. Mucinous cystadenomas, which account for 10-15% of benign ovarian tumours, have been reported to cause hyperandrogenic states and virilisation.<sup>[3]</sup> These tumours can however exhibit oestrogen producing capacities.<sup>[4]</sup> The improvement of genital phenotype in our baby, with time and contemporaneous to falling oestrogen levels, led to the clinical team attributing the cause to maternal hormonal effect on the foetus. A coordinated and structured approach toward examination and diagnostic testing would go a long way in allaying anxiety and providing precise prognosis.<sup>[5]</sup> In this patient, the final diagnosis was a genetic Androgen insensitivity syndrome. Androgen insensitivity syndrome (OMIM#300068), Partial Androgen insensitivity (OMIM#312300) and X-linked Hypospadias 1 (OMIM#300633) are caused by mutations in the AR gene (OMIM\*313700).<sup>[6]</sup> X-linked recessive disorder in which affected males have undervirilised external genitalia, later female breast development, absent uterus and female adnexa, and abdominal or inguinal testes, despite a 46,XY karyotype. Partial androgen insensitivity, also called Reifenstein syndrome, present as hypospadias and micropenis. These individuals produce age-appropriate androgen levels, but genital morphology depends on androgen receptor function.<sup>[7]</sup>

In this baby, it however remains to be seen what would be the effects of the additional problem: High female sex hormone exposure in early foetal life on the brain of the male foetus.

## CONCLUSION

We describe a 46XY neonate with features of undervirilisation. The mother had hyperoestrogenic state during pregnancy and this was attributed as the cause for the fetal DSD. However a systematic and step-wise workup revealed an underlying genetic cause. This case report emphasizes the need to follow a structured investigation strategy toward appropriate diagnosis and management.

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