Received: 17.7.2007 **Accepted: 2.2.2008**

Case Report

Male-like external genitalia with epididymis in a case of 46, XX disorder of sex development due to congenital adrenal hyperplasia

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Abstract

A case of five and half-year-old 46,XX phenotypic male with hyper pigmented empty scrotum, penile urethra, epididymis along with fallopian tubes, uterus and upper vagina as well as ovary is described. Hormonal studies were consistent with the diagnosis of congenital adrenal hyperplasia. The case represents the first documented case of 46,XX disorder of sex development due to virilizing CAH associated with differentiation of Wolffian ducts into epididymis.

KEY WORDS: 46,XX, virilization, external genitalia, epididymis, congenital adrenal hyperplasia

JRMS 2008; 13(3): 141-145

Ambiguous genitalia in 46,XX female is caused by early antenatal exposure to androgen from fetal adrenals, [1,2] fetal aromatase deficiency, [3,4] maternal androgen producing tumors, [5,6] maternal exogenous androgen exposure, [7,8] Wnt-4 mutation [9-11] or as associations. [12-14] The commonest cause is virilizing congenital adrenal hyperplasia (CAH) due to 21 hydroxylase deficiency [2]. Here the affected female is typically born with varying degree of ambiguity of external genitalia including occasional complete masculinization of the external genitalia and feminine internal genitalia. [8,15] Wolffian duct differentiation is consistently absent. [16] Male internal genital structures viz. seminiferous tubules, epididymis, vas deferens, seminal vesicles and ejaculatory ducts are developed from the Wolffian ducts. These structures are usually not virilized, presumably because they require markedly higher local concentrations of testosterone. This is supported by animal studies showing that unilateral castration causes ipsilateral Wolffian duct involution [17]. Till now there is no report of Wolffian ducts differentiation in female with virilizing CAH although it has been mentioned in the text book. [18] Nevertheless, severely affected females may occasionally have some development of typical male internal genital structures viz., prostate [19-21] and carcinoma of prostate. [22] Similarly, in female fetus of primates, [23] marsupials [24-26], hyena, [27,28] rat, [7,8] mouse, [29] mole, [30] etc. exogenous and/or endogenous androgen produce Wolffian ducts differentiation. Here, we report a case of 46,XX disorder of sex development due to CAH that presented with epididymis and male like external genitalia along with normal Müllerian ducts and ovaries.

Case Presentation

FPH26, reared as male, presented at the age of 5 years and 6 months with precocious puberty in the form of pubic hair growth, penile

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growth, growth spurt and aggressive behavior. The patient was born at term in home to non-consanguineous parents aged 26 (father) and 22 (mother) years. Antenatal period was uneventful. The past medical history revealed several attacks of diarrhea and vomiting since the second week of birth that required hospitalization as well as intravenous fluids 3-4 times as part of symptomatic management. No definitive diagnosis was made possible during several hospital admissions in infancy. There was no similar history in sibs or other family members. Physical examination showed normal vital signs. Patient was 110 cm tall (> 90th percentile) and weighed 18.1 kg (55th percentile). Secondary sexual characteristics were well developed; e.g., appearance of moustache, sideburns, pubic hairs (Tanner stage III) [31] and axillary hairs. There was no gynaecomastia. External genitalia was male-like except for bilateral cryptorchidism. Penis was 8 cm with penile urethra (Prader stage V). [32] Cytogenetics study (GTG banded chromosomes; ~350 band resolution) showed 46,XX chromosome complement. Bone age was corresponding to 10 years at chronological age of 5½ years (i.e., markedly advanced). Müllerian structure (uterus) with pelvic gonads was seen on pelvic ultrasonography. Abdominal ultrasonography did not reveal any adrenal tumor. Testosterone, 17 hydroxy-progesterone and luteinizing hormone were measured by radioimmunoassay. Testosterone was 16.56 nmol/L (adult male value 10.4-34.7 nmol/L), 17 hydroxyprogesterone was > 69 nmol/L i.e., beyond the maximum limit of laboratory (normal value: 0.1 - 3.1 nmol/L) and LH was 4 IU/L (adult male value: 5-20 IU/L). Serum electrolytes were normal. Plasma renin, aldosterone, ACTH, androstenedione, ACTH stimulation test/synacthen suppression tests and 21-hydroxylase gene mutation analysis were not carried out due to lack of facility. Diagnosis of simple virilization type of 21 hydroxylase-deficiency was made on the basis of clinical and laboratory findings and put on supplementation. Follow-up showed normalization of serum testosterone as well as 17 hydroxyprogesterone levels. As sex of rearing was male with well developed phallus and unambiguous penile urethra, it was felt that feminization would be unjustifiable. Parents were also insisted to continue with male sex. Laparotomy was planned for total hysterectomy with removal of appendices (uterus, tubes and ovaries) to prevent feminization in puberty. Total hysterectomy with appendices showed normally developed uterus, fallopian tubes and ovaries. Histological examination revealed presence of epididymis (figures 1, 2 and 3) but no seminiferous tubules in mesosalpinx at the level of ampulla of fallopian tube in addition to normal uterus, fallopian tubes and ovaries. Ovaries contained both stromal cells and follicles with germ cells (figure 4). No testicular tissue was found despite examining several sections of both gonads. Immunohistochemical studies to confirm epididymis (viz. androgen receptor antibody) were not carried out because functioning androgen receptors are widely present in female reproductive tract and they are susceptible to the masculinizing effects of androgens. [33]

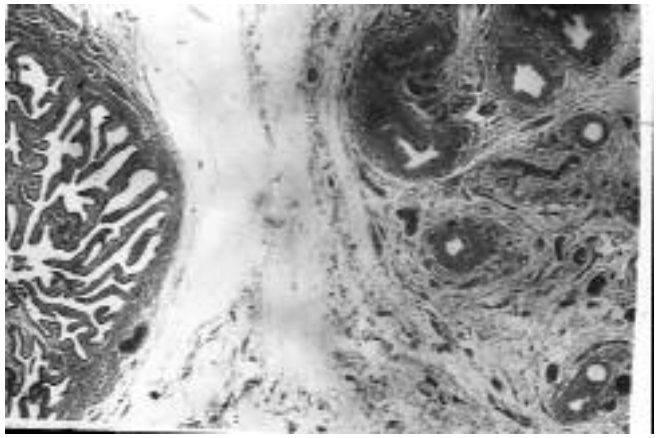

Figure 1. Microphotograph showing transverse section of ampulla of fallopian tube along with tubules of epididymis in one microfield. Note both Müllerian and Wolffian ducts in the same matrix (tissue section) and without any intervening serosal/peritoneal layers ruling out artifact (H & E X100).

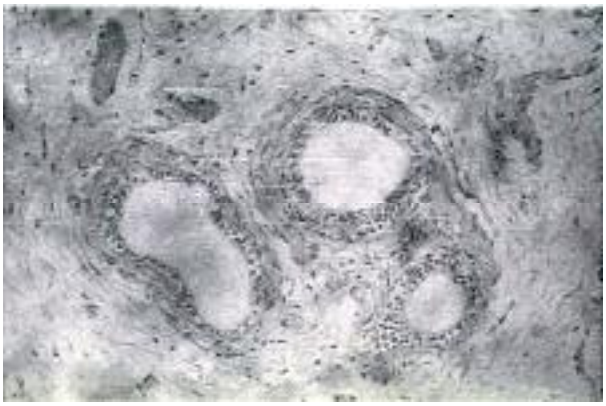

Figure 2. Microphotograph showing epididymis lined by cuboidal epithelium and wide lumen (H & E X200).

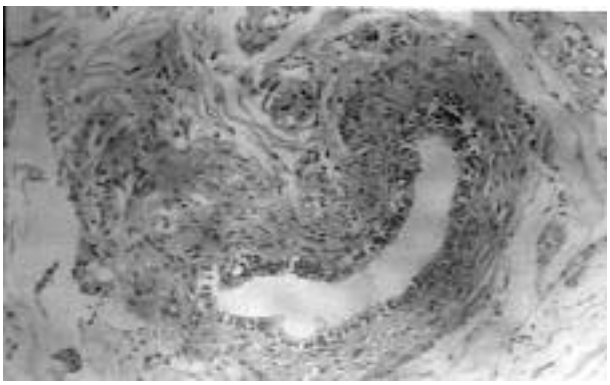

Figure 3. Microphotograph showing epididymis lined by cuboidal epithelium and wide lumen. Note smooth muscle bundles, which is characteristic of epididymis (H & E X400).

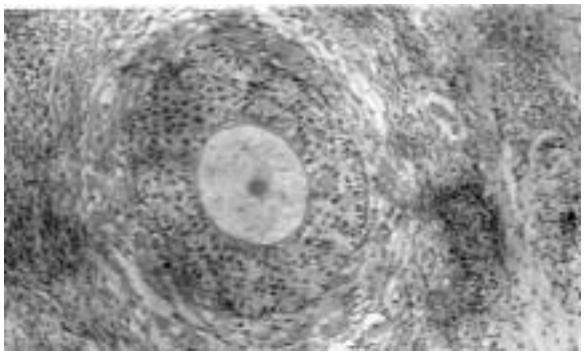

Figure 4. Microphotograph showing part of ovary containing germ cell along with ovarian stroma (H & E X200).

Discussion

The patient reported here represents a case of 46,XX disorder of sex development due to virilizing CAH associated with differentiation of Wolffian ducts into epididymis. Although Wolffian duct differentiation into epididymis in human female is not yet reported, it can be achieved in experimental model by various ways. In an experiment with marsupials, Shaw et al. (1988) [34] investigated the effects of oral androgen treatment of female tammar wallaby from day of birth (gonads were undifferentiated) to day 25 of pouch life (Wolffian & Müllerian ducts differentiated) and found greatly enlarged as well as patent Wolffian ducts along with male like phallus (endocrine effect). The treatment had no apparent effect on ovarian development or position. Similarly, Jost et al (1973) [35] showed that implantation of a crystal of testosterone or grafting of fetal testis adjacent to fetal rabbit ovary (female fetus) stimulates differentiation of male duct on that side (paracrine effect) and to a lesser extent on the contra-lateral side (endocrine effect). Although some experimental studies [36] demonstrated the regression of Müllerian duct following in-utero exposure of high dose testosterone during critical period of sex differentiation in female fetus, we did not find any such effect of testosterone on Müllerian duct in our case. Finding both Wolffian and Müllerian ducts together as in our case is also possible with ovotesticular disorder of sex development (previously true hermaphroditism), anti-Müllerian hormone deficiency syndrome, gonadal dysgenesis or androgen insensitivity syndrome. However, the possibilities of ovotesticular disorder of sex development (true hermaphroditism), gonadal dysgenesis, anti-Müllerian hormone deficiency syndrome or androgen insensitivity syndrome do not arise in our case as the patient's gonads were normal ovaries without any testicular tissue/dysgenetic gonad/ovotestis. The cause of Wolffian duct maturation and extreme virilization of external genitalia in our case was due to high fetal adrenal androgen and effects exerted through endocrine mechanism rather than paracrine mechanism (adrenals far from developing Wolffian ducts). The main point comes out from the case is that strongly virilized female can have such a high androgen concentration that is enough to initiate differ-

entiation of Wolffian ducts at least into epididymis. The lack of report reflects that these patients are usually diagnosed early and raised as girls, therefore internal sex organs are not evaluated at all. In severe virilizing CAH, similar findings may be seen more often if internal genital structure examined carefully routinely. We propose that very high level of systemic testosterone in embryonic period in female can differentiate Wolffian ducts by endocrine effect.

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