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CASE REPORT

Successful treatment with ICSI of infertility caused by azoospermia associated with adrenal rests in the testes

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Congenital adrenal hyperplasia (CAH) is a well-recognized, but uncommon, cause of azoospermia and infertility in men. Commonly this is due to undertreatment of excessive adrenal androgen secretion which suppresses gonadotrophin stimulation of the testes. A less common complication of CAH is development of adrenal tissue within the testes; this is important to recognize because it may be confused with malignancy leading to unnecessary surgery. In this case report, a man is described with simple virilizing CAH due to 21-hydroxylase deficiency who presented with azoospermia and was found to have adrenal rests. Investigations concluded that there was adequate adrenal suppression with glucocorticoids and that azoospermia was due to obstruction by adrenal rest tissue, strategically situated at the hilum of the testes. Spermatozoa were able to be retrieved by testicular aspiration from the man and these were used to successfully establish a pregnancy using intracytoplasmic sperm injection of his wife's oocytes.

Key words: adrenal rests/azoospermia/congenital adrenal hyperplasia/intracytoplasmic sperm injection

Introduction

Congenital adrenal hyperplasia (CAH) results from a genetic mutation which produces a deficiency of one of the steroidogenic enzymes in the adrenal glands. The commonest abnormality is 21-hydroxylase deficiency occurring in between 1 in 10 000 and 1 in 20 000 births (Pang and Clark, 1993; Thil'en *et al*., 1998). This results in reduced cortisol synthesis, increased adrenocorticotrophic hormone (ACTH) secretion and excessive adrenal androgen production. In a survey of women with this condition, only 20% achieved a pregnancy (Mulaikal *et al*., 1987); this was attributed to a number of factors including reduced heterosexual activity, inadequate vaginal reconstruction and sub-optimal hormone replacement. Infertility in men with CAH is less common, though azoospermia resulting from gonadotrophin suppression by excessive adrenal androgens is well described (Wischusen *et al*., 1981; Augarten *et al*., 1991; Mirsky and Hines, 1989; Valentino *et al*., 1997) and is important to recognize because it is a reversible form of infertility.

CAH in males may also be associated with bilateral testicular tumours, due to growth of ACTH-dependent adrenal tissue (Cutfield *et al*., 1983; Cunnah *et al*., 1989). Clinically, these tumours may present as painful, enlarged, irregular testes which may initially be confused with Leydig cell tumours (Kovacs and Asa, 1998). However, histologically adrenal rests lack Reinke crystalloids, they are bilateral and not autonomous and adequate suppression of ACTH by exogenous glucocorticoids may lead to a dramatic reduction in tumour size (Cutfield *et al*., 1983; Oberman *et al*., 1993). In this report, we describe persistence of adrenal tumours in the testes and azoospermia, despite more than adequate glucocorticoid treatment. This was confirmed by estimation of steroid hormones from gonadal vein samples and by testicular biopsy. Since normal spermatogenesis could be demonstrated in some areas of the testes on biopsy, it was concluded that obstruction was the most likely cause of azoospermia. It was possible to retrieve mature spermatozoa from the testes by aspiration and these were used to fertilize his wife's oocytes to achieve a successful pregnancy.

Case report

A 29 year old man was referred for investigation and management of azoospermia. His wife had been unable to conceive over 12 months despite having regular ovulatory cycles and regular intercourse during the peri-ovulatory period.. At the age of 6 months, he was diagnosed with a non-salt losing form of congenital adrenal hyperplasia due to 21-hydroxylase deficiency. During childhood and adolescence his management was supervised by paediatric endocrinologists in a specialized clinic, but his control was variable because of poor compliance with medication. By the age of 6 years, his bone age was advanced by three years and it remained so throughout child-

Table I. Baseline hormone concentrations whilst taking prednisolone

Investigation	Results	Reference range
17-OHP (nmol/l)	8	<6
ACTH (ng/l)	10.4	10–60
Testosterone (nmol/l)	11	10–25
SHBG (nmol/l)	26	7–40
DHEA-S (μmol/l)	0.2	2.6–14.0
Cortisol (nmol/l)	<20	190–690
Prolactin (mIU/l)	149	30 –450
LH (IU/l)	7	1–6
FSH (IU/l)	8	1–10

The reference ranges are those quoted by the kit manufacturers as follows: cortisol, TDX FLX System, Abbott Laboratories, North Ryde, NSW, Australia; ACTH, Immolite analgen, Diagnostic Products Corp., Los Angeles, CA, USA; DHEA-S, DHEA-S-7-RIA, Diagnostic System Lab., Parramatta, NSW, Australia; aldosterone, Coat-a-Count, Diagnostic Products Corp.; 17-OHP, Coat-a-Count, Diagnostic Products Corp. LH, FSH and prolactin are Bioclone IRMA kits, Marrickville, NSW, Australia. We have established a local reference range for males between 20 and 40 years. 17-OHP = 17-hydroxyprogesterone; ACTH = adrenocorticotrophic hormone; SHBG = sex hormone binding globulin; DHEA-S = dehydroepiandrosterone sulphate.

hood. Puberty began spontaneously at age 11 years and his growth ceased at 14 years of age. During his adolescent years, his compliance was quite irregular, but following his marriage at the age of 22 years, his medication was supervised by his wife. He had taken prednisolone, 10 mg twice a day, regularly since that time.

On examination, he was mildly obese and Cushingoid. His height was 167 cm (10th centile) and weight was 85 kg. His mid-parental height was 177 cm, though he has a brother who is 185 cm (90th centile). His blood pressure was 130/80 without a postural drop and he had normal secondary sexual characteristics without gynaecomastia. Both testes were abnormal to palpation, being nodular and hard with a volume in excess of 25 ml. The vas deferens and epididymis were palpable on both sides and were normal.

A clinical diagnosis of congenital adrenal rests in the testes was made and this was supported by typical changes on a testicular ultrasound showing bilateral hypoechoic intratesticular masses which were heterogeneous and of increased vascularity (Vanzulli *et al*., 1992; Avila *et al*., 1996). These measured 2 cm on the right and 0.5 cm on the left. The remaining testicular tissue showed irregular hyperechoic regions consistent with fibrosis. Initial biochemical investigations were performed whilst this patient was receiving his usual dose of prednisolone and these results confirmed near-complete suppression of the hypothalamic-pituitary-adrenal axis, with normal concentrations of gonadotrophins and serum testosterone (Table I).

Although our patient had a serum concentration of 17-hydroxyprogesterone which was above the normal reference range (<6 nmol/l), the range in untreated patients with congenital adrenal hyperplasia is between 350 and 500 nmol/l (Young *et al*., 1994). It is generally accepted that suppression of 17-hydroxyprogesterone into the normal range can only be achieved in patients with congenital adrenal hyperplasia by giving supraphysiological doses of glucocorticoids (Iippe *et al*., 1974; Hughes *et al*., 1976). This patient's low serum concentration of 17-hydroxyprogesterone is consistent with his low serum cortisol, DHEA and ACTH (Table I) and indicate major suppression of the hypothalamic-pituitary-adrenal axis.

In order to confirm the adrenal nature of the testicular masses, venous samples were collected, with the patient's consent, from the inferior vena cava, the left testicular and the left adrenal veins before and 30 min after i.v. injection of synthetic ACTH (Tetracosactrin 250 μg; Novartis Pharmaceuticals, North Ryde, NSW, Australia); at the time of study the patient had been without his normal medication for 18 h. Samples were assayed for hormones by established radioimmunoassays (Table II). In addition, immunoreactive inhibin B was assayed using an inhibin B specific enzyme-linked immunosorbent assay (Groome *et al*., 1996) and also by a radioimmunoassay which measures both inhibin and free α subunit products (Robertson *et al*., 1989). The results showed low concentrations of serum ACTH, cortisol and dehydroepiandrosterone sulphate (DHEA), even in adrenal vein samples, which is consistent with long-term suppression of endogenous ACTH. The poor response of cortisol to ACTH is in keeping with this and with deficiency of 21-hydroxylase. Plasma aldosterone concentrations were well maintained, consistent with absence of clinical symptoms of salt deficiency and in keeping with normal activity within the zona glomerulosa of 21-hydroxylase. Following ACTH, there was a small increase in adrenal vein testosterone, but its contribution to the overall peripheral concentration, compared to the gonad, was small. Gonadal vein testosterone concentrations were normal, in keeping with non-suppressed gonadotrophin concentrations.

It was clear that the testes contained functioning adrenal tissue since gonadal vein samples showed substantial amounts of cortisol and aldosterone and these concentrations increased further after ACTH stimulation (Table II). It is of interest that this tissue, like the normally placed adrenal gland, also lacked the 21-hydroxylase enzyme because basal and stimulated concentrations of 17-hydroxyprogesterone are comparable to those found in the adrenal vein. This is consistent with direct measurement· of 21-hydroxylase activity reported in the in-vitro study of a similar tumour (Clark *et al*., 1990).

Basal samples from gonadal and peripheral veins showed similar concentrations of inhibin B and ACTH caused no significant change. However, when measured in the assay which includes α subunits, gonadal vein concentrations were higher in the basal state than in peripheral samples and there was a significant increase after ACTH (Table II). A few days after recovery from this investigation, a 5000 IU human chorionic gonadotrophin (HCG) stimulation test was performed which showed a normal testosterone response, consistent with normal leydig cell function (Table III) (Padron *et al*., 1980). Inhibin B concentrations in the peripheral vein sample did not change after HCG, but the less specific assay showed a definite increase in inhibin.

Biopsy of the major nodule, with the patient's informed consent, showed that it was composed of tissue principally resembling adrenocortical cells. However in some areas, these cells were interspersed with hyalinized outlines of seminiferous tubules that lack an epithelium and in other areas with identifiable seminiferous tubules showing a severely reduced

Table II. Hormone concentrations in samples collected from the inferior vena cava, the left adrenal vein and the left gonadal vein before and 30 minutes after synacthen injection (250 μg i.v.).

	Peripheral		Adrenal		Gonadal	
	Basal	Post ACTH	Basal	Post ACTH	Basal	Post ACTH
ACTH (ng/l)	10.4		<10		12.5	
Cortisol (nmol/l)	30	<20	<20	80	20	70
17-OHP (nmol/l)	11.5	54.6	235	>600	348	>600
DHEA-S (pmol/l)	<0.2	<0.2	<0.2	<0.2	0.2	<0.2
Aldosterone (ng/100 ml) (supine)	5	14	48	>120	35	94
Test (nmol/l)	13.0	15.0	8.4	20.0	244	295
Oestradiol (pmol/l)	60	70	<50	50	240	250
Inhibin (IU/l)	289	244			366	495
Inhibin B (pg/ml)	96				85	83

For abbreviations, see Table I.

Table III. Hormone concentrations before, 2 days and 4 days after an i.m. injection of 5000 IU human chorionic gonadotrophin

	Day 0	Day 2	Day 4	Reference range
Testosterone (nmol/l)	15	32	27	10–25
Oestradiol (pmol/l)	55	135		<100
Inhibin (U/l)	241	401	459	230–870
Inhibin B (pg/ml)	81	83	85	43–390
LH (IU/l)	15	5	4	1–6
FSH (IU/l)	12	8	4	1–10

The reference ranges for testosterone and oestradiol are those quoted by the kit manufacturers (Elecys Immunoassay, Roche Diagnostics Corp., Castle Hill, NSW, Australia; RIA oestradiol-2 assay, DiaSorin S.R.L., Vercelli, Italy).
The inhibin B assay is described in the text. The normal range from David DeKretser's laboratory is based on series of 39 normal young men.

complement of germ cells. In a biopsy taken away from the site of the nodules, the seminiferous tubules were of normal diameter with all stages of germ cell development present, including plentiful elongated spermatids. The numbers of germ cells varied from being normal to a moderate degree of hypospermatogenesis. Normal Leydig cells were identified in the intertubular tissue.

The man's glucocorticoid dosage was reduced to prednisolone 10 mg taken at 2200 h and 2.5 mg at 0800 h. After 6 months, his semen analysis remained unchanged. Samples of stored spermatozoa did not thaw successfully, so a needle aspiration of the testes was performed and motile spermatozoa obtained from this sample were used for intracytoplasmic sperm injection into his wife's oocytes (Van Steirteghem *et al*., 1993). A successful singleton pregnancy was achieved in the first cycle of treatment and a normal male child with a birthweight of 2640 g and Apgar scores of 9 and 10 was delivered at 33 weeks gestation. The neonatal course was uneventful.

Discussion

Although the finding of enlarged, irregular testes in a man with infertility usually raises concern about malignancy, a history of congenital adrenal hyperplasia is more suggestive of the presence of benign adrenal rests. Palpable testicular nodules have been described in up to 24% of male patients with CAH (Avila *et al*., 1996) and these are detected even more commonly by the use of magnetic resonance imaging or ultrasound (Avila *et al*., 1999). In this patient, the adrenal nature of the nodules was demonstrated by the finding of cortisol and aldosterone secretion in the gonadal vein samples which increased after ACTH stimulation.

Aberrant adrenal tissue has been described in up to 50% of newborn infants but it usually atrophies within a few years (Schechter, 1968). Adrenal rest tumours are a complication of conditions with uncontrolled ACTH secretion such as Addison's disease (Cohen, 1946), Cushing's disease (Hamwi *et al*., 1963), Nelson's syndrome (Verdonk *et al*., 1982) and glucocorticoid resistance (Chroussos *et al*., 1993). They are a well-recognized complication of both the salt-losing and simple virilizing forms of 21-hydroxylase deficiency (Willi *et al*., 1991), as well as other forms of congenital adrenal hyperplasia (Srikanth *et al*., 1992).

The origin of these tumours is still debated but it is generally accepted that they are derived from ectopic adrenal cells which migrate with primitive gonadal cells from the urogenital ridge at around of 8 weeks of fetal development (Schechter, 1968). In support of this, aberrant adrenal tissue has been described along the path of migration in the kidney, supradiaphragmatic

region, the spermatic cord and the testes (Ventura *et al*., 1998), as well as in various parts of the female genital tract. Adrenal rest cells retain ACTH receptors, and, under continued stimulation by ACTH, they may become adenomatous although this is usually a late finding. More commonly, adequate suppression of nocturnal hypersecretion of ACTH by a late evening dose of synthetic glucocorticoid will cause regression in tumour size and restoration of spermatogenesis (Cunnah *et al*., 1989). In the patient in this report, however, large nodules persisted in both testes despite compliance with treatment and he remained azoospermic and infertile, a situation in keeping with previous reports (Bonaccorsi *et al*., 1987; Keely *et al*., 1993). This is a recognized complication of previous poor control of CAH and is an indication of adenomatous transformation of the adrenal rests (Rutgers *et al*., 1988; Clark *et al*., 1990; Blumberg-Tick *et al*., 1991).

In the patient, the testicular biopsy showed areas of normal spermatogenesis in parts of the testes distant from the adrenal rests, although there was a reduction in germ cells and hypospermatogenesis was a feature in areas closer to the hilum. The degree of normal spermatogenesis, confirmed later by the ease of obtaining viable spermatozoa by testicular biopsy, combined with the total absence of spermatozoa from the ejaculate on a number of occasions, suggested that obstruction was the most likely cause of azoospermia and infertility in this man. Given the propensity of adrenal rests to develop close to the hilum of the testes, it was postulated that this strategic placement caused obstruction to small efferent ducts carrying spermatozoa, either as a result of the relatively inelastic structure of the tunica albuginea or by reduced local blood supply in this area. An alternative theoretical cause for azoospermia is that local adrenal steroids or metabolites derived from the adrenal rests are toxic to Sertoli or germ cells, as has been proposed to explain spermatogenic abnormalities in some men with varicoceles (Comhaire and Vermeulen, 1974; Takihara *et al*., 1991). Although there was evidence of hypospermatogenesis in some areas of the biopsy, this was not widespread and Sertoli cell function was normal, as judged by the measurement of peripheral and gonadal vein inhibin B concentrations.

It is of interest that concentrations of inhibin B did not alter significantly in either gonadal or adrenal vein samples after injection of ACTH or HCG. However, there was a significant increase when the samples were assayed for both dimeric inhibin and the free α subunit. This is interpreted this to mean that it is the free α subunit which is increased in these samples and that it is produced by both Leydig cells and the adrenal cortex. This conclusion is in keeping with the studies demonstrating that the adrenal cortex can secrete free α subunits (Crawford *et al*., 1987; Nishi *et al*., 1995) and with the observation that free α subunit increases after HCG in a normal man (McLachlan *et al*., 1988).

Although rare, a history of congenital adrenal hyperplasia should be sought in all men with azoospermia or with an incidentally discovered testicular mass and the relevant investigations should be performed when this possibility is raised. There is a tendency to concentrate medical attention on children with CAH, particularly those with salt-losing forms of the condition. This case, however, emphasizes the need for adolescent patients to be carefully handled during the transition to adult care. There is clearly a need for continued control of CAH throughout adult life, even if salt wasting is not a clinical problem. Finally, in men with CAH whose azoospermia persists despite adequate glucocorticoid treatment, it might still be possible to recover testicular spermatozoa, and, as this case illustrates, this can be used successfully in conjunction with assisted reproductive technology to restore fertility.

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