

## Bilateral gonadoblastoma/dysgerminoma in a 46 XY individual: case report with hormonal studies

RA FISHER, R SALM,\* RW SPENCER

*From the Departments of Chemical Pathology and Histopathology, Royal Cornwall Hospital (Treliske), Truro, Cornwall*

**SUMMARY** A case of bilateral gonadoblastoma/dysgerminoma in a 46 XY phenotypical female is presented. Increased circulating  $\beta$  human chorionic gonadotrophin ( $\beta$ -HCG) and testosterone together with a decreased concentration of follicle stimulating hormone (FSH) reflected the activities of these tumours. The patient is alive and well three years later, after treatment by surgery and cobalt therapy.

The occurrence of gonadoblastoma/dysgerminoma in phenotypical females who are chromosomal males has been well documented by Scully,<sup>1</sup> but detailed hormonal data have been recorded in comparatively few cases. We therefore report such a patient in whom relevant endocrinological assays have been carried out, although our investigations were restricted by the patient presenting as a surgical emergency while on holiday and subsequently returning to her home county.

### Case report

A 20-year-old woman was admitted in November 1977 with pain in her left iliac fossa of four days' duration. Examination showed her to be a 1.83 m tall phenotypical female of slim but somewhat masculine build with square shoulders, moderately heavy lower jaw and elongated fingers. Her voice was of female pitch. There were mild facial hirsutes and acne, but otherwise her hair distribution was of female type. Her breasts were developed but small, and the distribution of fat about her hips was masculine in type.

There was tenderness and guarding on the left, and rebound tenderness on the right side of the abdomen. Her vulva was normal, but her clitoris was enlarged measuring 2 cm in length. Her vagina was of normal length and capacity and a normal cervix was palpable in the vault. Separately from the cervix, there was an abdominal mass of the size of a 16 weeks' pregnancy. At laparotomy a little clear ascitic fluid was present in the peritoneal cavity and

a small normal uterus was noted, but male internal genital organs were not identified. The gonadal sites were occupied by encapsulated masses with thin fibrinous adhesions to surrounding structures: one of these masses was firmly wedged in the pelvis. The Fallopian tubes were elongated and stretched over these tumours, but there was no evidence of intra-abdominal neoplastic spread. A bilateral salpingo-oophorectomy was carried out. Post-operative recovery was uneventful. Subsequently the patient received cobalt therapy to her abdomen, and has now remained well for three years.

### PREVIOUS HISTORY

At the age of 15 the patient had sought medical advice about her continuing growth, but as she was one of a family of tall children, this was regarded as constitutional. At that time her breasts were recorded as prepubertal.

Her menarche had occurred at the age of 16, but her periods had always been irregular, occurring at two to three months' intervals, and the loss had always been scanty, requiring never more than two Tampax a day. She had never received any hormone treatment and her last period had occurred three weeks before admission.

### OPERATION SPECIMENS

The two encapsulated ovoid tumours were received fixed in formalin, the elongated Fallopian tubes being stretched over their peripheries. The right mass measured 15 × 12 × 10 cm and the left mass 14 × 11 × 9 cm and weighing 800 g and 620 g respectively. On slicing, the cut surfaces were homogeneous, pinkish-grey and firm-elastic. No ovarian or testicular tissue was identifiable.

Microscopically, the bulk of both tumours showed

\*Present address: Histopathology Department, Royal Postgraduate Medical School, Hammersmith Hospital, Duane Road, London W12 0HS.

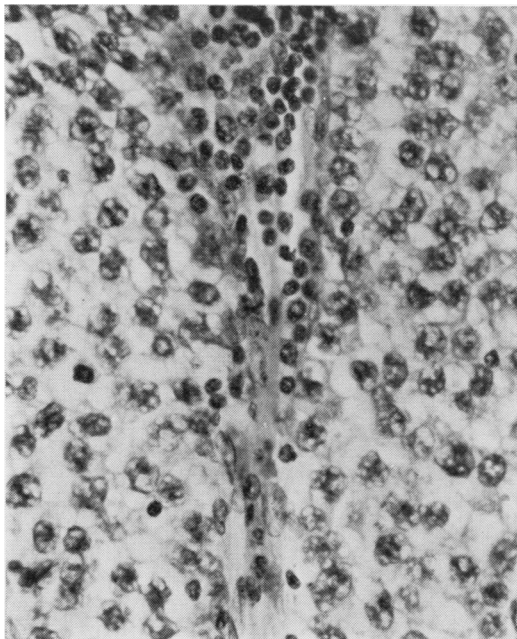


Fig. 1 Typical seminomatous appearance of bulk of tumours. Haematoxylin and eosin  $\times 400$ .

the typical features of seminomas (dysgerminomas) (Fig. 1) with focal invasion of their fibrous capsules. There were occasional syncytial giant cells, but Leydig cells were not found. At the periphery of the right mass there was a short fibroblastic strip with nodular calcification, resembling tissue of a gonadal streak or superficial ovarian cortex (Fig. 2). Below

the fibrous capsules there were numerous scattered nodular calcifications, some of which were engulfed by seminomatous growth. Most of these calcifications were adjoined by typical, round, oval or elongated nests of gonadoblastoma (Fig. 3). These were composed of two distinct cell types, the one resembling immature Sertoli or granulosa cells with dark-staining, elongated nuclei and ill-defined cytoplasm, the second cell type being large and spheroidal, with round nuclei and foamy or vacuolated cytoplasm and a mitotic rate of about two per ten high power fields, bearing a close resemblance to the cells of the dysgerminoma. These cells were arranged around small, round, hyaline, eosinophilic, PAS-positive bodies giving the tumour a pseudofollicular appearance.

#### LABORATORY INVESTIGATIONS

Venous blood was examined by conventional and chromosome banding techniques and showed a normal male 46 XY karyotype. The Y chromosome had a normal morphology and there was no evidence of mosaicism. Radioimmunoassay kits were used to measure luteinising hormone (LH), FSH, prolactin (manufactured by CIS and supplied by Eurotope Services Ltd) and human growth hormone (HGH) (Phadebas PRIST, Pharmacia (Great Britain Ltd)). HCG is directly equivalent to LH in the LH assay but exhibits no cross reaction in the FSH assay. Plasma and urine free cortisol were measured by a competitive protein binding procedure (Cortipac, Radiochemical Centre, Amersham). Plasma testosterone, oestradiol,  $17\alpha$ -hydroxyprogesterone and  $\beta$ HCG were measured by specific radioimmunoassays at various SAS centres. Urinary pregnanetriol

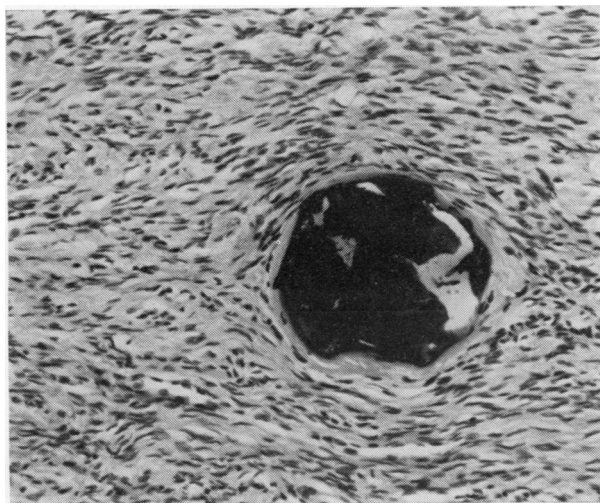


Fig. 2 Fibroblastic streak from periphery of right mass with nodular calcification. Haematoxylin and eosin  $\times 150$ .

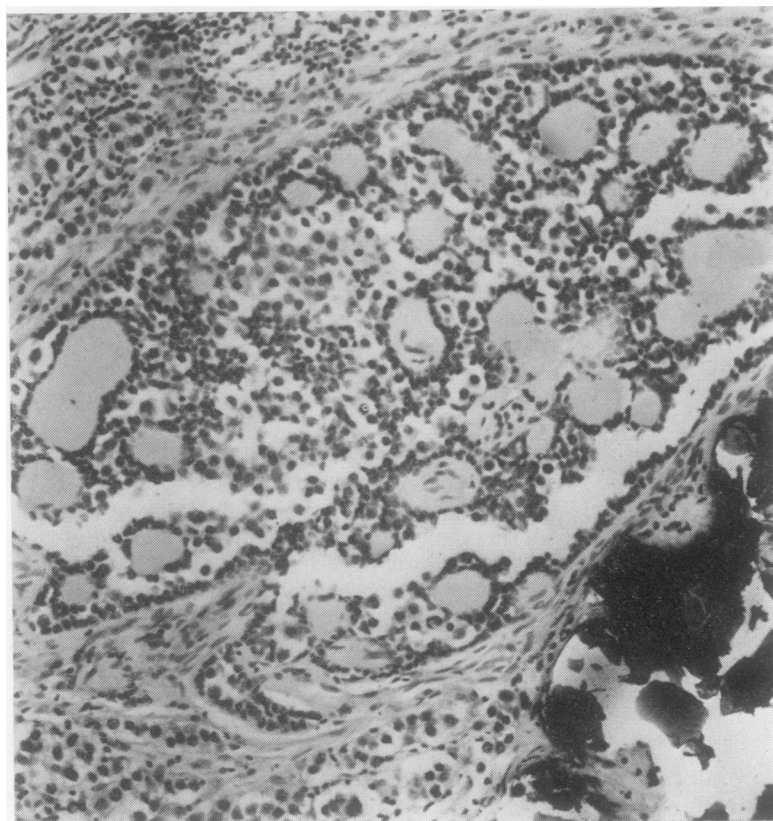


Fig. 3 *Elongated nodule of gonadoblastoma with adjacent calcification engulfed by seminomatous tumour. Haematoxylin and eosin, original magnification  $\times 200$ .*

was measured colorimetrically.<sup>2</sup> Routine Auto-analyzer methods were used to measure urea, electrolytes and glucose.

Pre- and postoperative hormone levels are shown in the Table. Preoperatively the patient had a very high level of LH which was almost certainly due to HCG ( $\beta$ -HCG was 136 U/l). The FSH was low while the plasma testosterone was about two and a half times greater than that expected in normal

women.

A significant decrease in LH and testosterone was found on the first postoperative day. For technical reasons it was not possible to review the  $\beta$ -HCG at this time. The increase in prolactin, plasma and urinary free cortisol were ascribed to stress. A normal HGH response to carbohydrate loading was later demonstrated. Plasma electrolytes, urea and glucose were normal.

#### Pre- and postoperative hormone levels

	LH IU/l*	FSH IU/l†	$\beta$ -HCG mIU/ml	Testosterone nmol/l	Oestradiol pmol/l	Prolactin mU/l	17 $\alpha$ OH progesterone nmol/l	Pregnanetriol (urine) $\mu$ mol/24 h	Free cortisol (urine) nmol/24 h
Normal range	1-11	3-11	< 2	$\delta$ 10.4-38.2 $\eta$ 0.5-2.1	$\eta$ Foll 70-260 Post-meno- pausal < 220	< 500	< 18	3.6-7.8	72-502
Pre-op	> 108	1.5	136	5.5	—	—	—	—	—
Post-op Day 1	29.5	2.2	—	0.4	64	—	—	1.8	—
Post-op Days 3-9	—	—	—	0.6	—	714	2	—	1193

\*Values expressed as IU/l of MRC 68/40.

†Values expressed as IU/l of MRC 68/39.

## Discussion

Gonadoblastoma occurs rarely in normal testes, less rarely in normal ovaries, and typically in dysgenetic gonads.<sup>3</sup> Although the bilateral tumours of our patient had occupied the normal ovarian sites, they had destroyed all evidence of the nature of the pre-existing gonadal tissue, and the finding of a fibroblastic strip is by itself, as Scully<sup>1</sup> emphasised, inconclusive evidence. XY chromosomes, as found in our patient, do not preclude the presence of a normal ovary, as has been found in a hermaphroditic infant with ovarian gonadoblastoma.<sup>4</sup> According to Mulvihill *et al*<sup>5</sup> the Y chromosome is a pre-requisite for the development of malignancy in a dysgenetic gonad, a risk which the authors calculated as being around 25%. Our patient's menstrual history of irregular, infrequent and scanty periods suggests that at least some functioning ovarian tissue had been present at one or both gonadal sites. It should be remembered, however, that gonadal streaks, such as found in our patient, as well as gonadoblastomas have been shown to be capable of producing both androgens and oestrogens *in vivo* and *in vitro*.<sup>6-9</sup>

In his review of 74 cases of gonadoblastoma, Scully<sup>1</sup> distinguished clinically virilised and non-virilised phenotypical females, as well as phenotypical males with various degrees of feminisation. Of the 35 virilised phenotypical females, all but one over the age of 15 complained of primary amenorrhoea, six had experienced vaginal bleeding and three had had normal cycles for various lengths of time. Breasts were mostly small. Four of the 25 patients in this clinical group had slightly raised 17-ketosteroids and the gonadotrophins were found to be raised in 17 of the 21 cases in which they were measured. Two patients were chromatin-positive and 30 were chromatin-negative. The karyotype of blood specimens in most cases was 46 XY. In seven further similar cases of gonadal dysgenesis in 46 XY phenotypical females with gonadoblastoma and dysgerminoma,<sup>10-15</sup> primary amenorrhoea was usual though not invariable, and breast development was mostly poor. Plasma testosterone was increased in half of the cases where measured, while both FSH and LH were reported as raised in the majority. The secretion of gonadotrophins immunologically and biologically similar to HCG in cases of dysgerminoma has also been documented.<sup>16</sup>

In our case breast development was also poor, but infrequent and scanty menstruation had occurred up to the time of laparotomy. Plasma testosterone and serum LH were both raised, the latter almost certainly due to cross-reactivity with a markedly

raised HCG (confirmed by specific  $\beta$ -HCG assay). Our finding of a low serum FSH is in agreement with previous reports of HCG-secreting tumours in both men and women.<sup>17 18</sup>

While it was not possible to measure plasma oestradiol in the available preoperative specimen, it seems reasonable to postulate a raised value due to at least some peripheral conversion of the increased circulating androgens. Earlier reports of raised FSH in these cases might have been due to technical limitations at the time.

In accordance with Scully's view<sup>1</sup> the germ cells of the dysgerminoma seem the most likely source of the HCG, whereas the increased androgens were probably produced by the cells of the gonadoblastoma. Both hormone levels fell markedly on complete removal of the gonadal masses. Our case supports Scully's view that gonadoblastomas should be regarded as *in situ* malignancies which, similar to *in situ* tumours at other sites, may become frankly invasive, usually by giving rise to seminomas (dysgerminomas). Our results suggest that the pattern of the hormonal changes reflects the activity of these tumours.

We are indebted to Brian Cox, FRCS, FRCOG, for the clinical data, to Dr Alan McDermott at the Cytogenetics Department, Southmead Hospital, Bristol for the chromosome studies, to Dr Tom Hargreaves at the Area Laboratory, Exeter for the measurements of pregnanetriol and to Mr W Hinkes at the Royal Postgraduate Medical School, London for the photomicrographs.

## References

- 1 Scully RE. Gonadoblastoma: a review of 74 cases. *Cancer* 1970;**25**:1340-56.
- 2 Morris R, Leeson JA. A comparison of two methods for the separate estimation of 11-deoxy and 11-oxygenated 17-hydroxycorticosteroids in urine. *J Med Lab Technol* 1969;**26**:243-7.
- 3 Hughesden PE, Kumarasamy T. Mixed germ cell tumours (gonadoblastomas) in normal and dysgenetic gonads: Case reports and review. *Virchows Arch (Pathol Anat)* 1970;**349**:258-80.
- 4 Park J, Pyeate JC, Jones HW, Woodruff JD. Gonadoblastoma in a true hermaphrodite with 46XY genotype. *Obstet Gynecol* 1972;**40**:466-72.
- 5 Mulvihill J, Wade WM, Miller RW. Gonadoblastoma in dysgenetic gonads with a Y chromosome. *Lancet* 1975; **i**:863.
- 6 Wieland RG, Ekstrom B, Vorys N. C<sub>19</sub>O<sub>2</sub> steroid secretion by dysgenetic gonads. *Obstet Gynecol* 1968;**32**:643-4.
- 7 Judd HL, Scully RE, Atkins L, Neer RM, Kliman B. Pure gonadal dysgenesis with progressive hirsutism. *N Engl J Med* 1970;**282**:881-5.
- 8 Mackay AM, Pettigrew N, Symington T, Munro Neville A. Tumours of dysgenetic gonads (gonadoblastoma) ultrastructural and steroidogenic aspects. *Cancer* 1974; **34**:1108-25.

- <sup>9</sup> Talerman A. Germ cell tumours of the ovary. In: Blaustein A, ed. *Pathology of the female genital tract*. New York, Heidelberg, Berlin: Springer-Verlag, 1977:574-5.
- <sup>10</sup> Cantu JM, Olivera E, Gonzalez D, Hidalgo F, Gonzalez M, Gallegos AJ. A possible explanation for spontaneous breast development in XY gonadal dysgenesis. *Ann Endocrinol (Paris)* 1972;**33**:517-22.
- <sup>11</sup> Palacios JM, Pato I, Garcia-Robles R. Dysgenesie gonadique 46-XY. *Nouv Presse Med* 1973;**2**:2822.
- <sup>12</sup> Anderson CT, Carlson IH. Elevated plasma testosterone and gonadal tumours in two 46XY "sisters". *Arch Pathol Lab Med* 1975;**99**:360-3.
- <sup>13</sup> McDonough PG, Ellegood JO, Byrd JR, Mahesh VB. Ovarian and peripheral venous steroids in XY gonadal dysgenesis and gonadoblastoma. *Obstet Gynecol* 1976;**47**:351-5.
- <sup>14</sup> Foulkes J, Nicholls PE. A case of dysgerminoma-gonadoblastoma in pure gonadal dysgenesis. *Aust NZ J Obstet Gynaecol* 1979;**19**:52-5.
- <sup>15</sup> Schokman FCM, Correy JF. A patient with pure gonadal dysgenesis, gonadal tumour and virilisation. *Aust NZ J Obstet Gynaecol* 1979;**19**:241-4.
- <sup>16</sup> Ross GT, Van de Wiele RL. The ovaries. In: Williams RH, ed. *Textbook of endocrinology*. 5th ed. Philadelphia, London, Toronto: Saunders, 1974:368-422.
- <sup>17</sup> Reiter EO, Kulin HE. Suppressed follicle stimulating hormone in men with chorionic gonadotrophin secreting testicular tumours. *J Clin Endocrinol Metab* 1971;**33**:957-61.
- <sup>18</sup> Reiter EO, Braunstein GD, Hamwood SM, Kulin HE. Suppressed follicle stimulating hormone (FSH) in women with gestational trophoblastic neoplasms. *J Clin Endocrinol Metab* 1973;**36**:697-701.

Requests for reprints to: Dr RW Spencer, Department of Chemical Pathology, Royal Cornwall Hospital (Treliske), Truro, Cornwall TR1 3LJ, England.