Benign Leydig cell tumour and germ cell carcinoma *in situ* in a young man with gynaecomastia

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Summary

A 21-year-old man presented with a 16-year history of recurrent pyrexial episodes and a 5-year history of gynaecomastia. Blood and urinary oestrogen levels were elevated and a mass was found in the upper pole of a retractile right testis.

After orchidectomy, oestrogen levels fell, gynaecomastia regressed and the pyrexial episodes ceased.

Histological examination of the right testis showed a benign Leydig cell tumour in the upper pole and a germinal cell carcinoma *in situ* in the remaining part of the testis. Thus a potentially lethal condition was detected at an early pre-malignant phase by virtue of a benign, endocrinologically active tumour. This would seem to be the first report of the co-existence of a Leydig cell tumour and germ cell carcinoma in the same testis.

KEY WORDS: Leydig cell tumour, testicular carcinoma, oestrogen, gynaecomastia, fever.

Introduction

Leydig cell tumours are rare, accounting for only 1.2% of testicular neoplasma (Collins and Pugh, 1964; Dixon and Moore, 1952). The age distribution is bimodal with peak incidences between 5-10 and 30-35 years. Feminizing signs are found in 20-25% (Daugaard and Hasselberg, 1957; Gabrilove *et al.*, 1975) but in the majority there are no endocrine manifestations. Although the overall incidence of testicular germ cell carcinoma *in situ* is not known, the condition is found in 8% of cryptorchid testes leading to invasive carcinoma in 70% of infertile men within 5 years of first biopsy (Skakkebaek and Berthelsen, 1978).

The unique features of the present case are the co-existence of a Leydig cell tumour and germ cell carcinoma *in situ* in the same testis and the 17-year

history of intermittent pyrexial attacks resolving after orchidectomy.

Case report

The patient was referred at the age of 21 years complaining of bilateral gynaecomastia since the age of 17 years and frequent attacks of a pyrexial illness during the past 16 years.

He was born as a result of a normal pregnancy and labour and there was no parental consanguinity. At the age of 5 years he first experienced a pyrexial illness, which then recurred regularly at 3- to 4-weekly intervals. Each pyrexial episode lasted 2 to 3 days and was accompanied by a sore throat and generalized aches and pains. Frequency and dysuria often occurred during the febrile attack. Innumerable medical consultations and full screening tests for pyrexia of unknown origin were made over 16 years but the cause of these episodes was never identified.

At the age of 10 years a school doctor noted that the right testicle was retractile, although similar in size to the left which remained firmly anchored in the scrotum. Secondary sexual characteristics developed at the age of 13 years and he then started shaving two to three times a week. At the age of 17 years gynaecomastia developed over a period of 9 months. Several medical consultations were sought because of this and the general conclusion was that the gynaecomastia was a pubertal phenomenon. Libido was unimpaired, he reported regular heterosexual intercourse and participated freely in competitive athletics.

On examination he was 162 cm tall, weighed 50 kg and was effeminate in manner. Bilateral gynaecomastia with approximately 4 ml of glandular breast tissue was present but there was no galactorrhoea. Pubic, axillary and facial hair were satisfactory but there was little trunk hair. The left testis was 2 inches

TABLE 1. Blood endocrine profile

	Pre-operative	Post-operative	Normal male range
Oestradiol	320	130	37–129 pmol/l
Testosterone	8.5	25	11–44 nmol/l
Prolactin	300	290	30–360 mu/l
SHBG	55	28	17–55
LHRH test			
LH (basal)	8.4	23.0	1–10 mu/l
LH (20' post LHRH)	22.0	165.0	
LH (60' post LHRH)	19.0	120.0	
FSH (basal)	0.9	10.0	1–7 mu/l
FSH (20' post LHRH)	1.5	27.0	
FSH (60' post LHRH)	1.4	24.0

FIG. 1. Longitudinal slice of testis and epididymis showing a solitary well-defined lobulated yellow tumour nodule at the upper pole of the testis. The tunica albuginea overlaying the tumour is intact and the spermatic cord normal.

in length; the right testis was retractile 1 inches long and showed a nodular mass on its upper pole. There were no other abnormal clinical signs.

Semen analysis on two occasions showed a few

non-motile spermatozoa only in the centrifuged deposit.

Endocrine assessment (Table 1) showed elevated blood and urinary oestrogens, a low blood testosterone and impaired follicle stimulating hormone (FSH) response after administration of luteinizing hormone releasing hormone (LHRH). Blood concentrations of chorionic gonadotrophin, α -feto-protein and human placental lactogen were within the reference range.

In view of the testicular mass, he was referred for orchidectomy. The procedure and post-operative recovery were uneventful. Further examination of the right testis, as described under Fig. 1, 2 and 3, showed a Leydig cell tumour in the upper pole and a germ cell carcinoma in the body of the testis.

After orchidectomy there was a dramatic fall in plasma oestrogen and a marked rise in testosterone. The LH and FSH response to LHRH became exaggerated. Plasma concentration of sex hormone

FIG. 2. High power view of the Leydig cell tumour which is composed of regular cells with rounded or oval nuclei with distinct nuclear membranes and one or more well-defined nucleoli. The cytoplasm is eosinophilic and granular and cytoplasmic borders are indistinct. Several blood vessels and two fibrous septae are also seen.

FIG. 3. High power view of the testis showing some sclerosed seminiferous tubules whilst others show prominent thickening of the basement membrane. Non-sclerotic tubules contain, adjacent to the basement membrane, large cells with clear cytoplasm, which is rich in glycogen, distinct cytoplasmic borders and slightly hyperchromatic nuclei. At the top of the picture similar cells can be seen extending in Pagetoid fashion with the rete testis between the columnar epithelium and basement membrane. The features are those of germ cell carcinoma *in situ*.

binding globulin (SHBG) fell post-operatively, but prolactin levels were unchanged (Table 1).

The gynaecomastia decreased and the patient became more masculine in attitude and bearing; he also developed facial acne.

Discussion

Germ cell carcinoma *in situ* is a pre-malignant condition, analogous to carcinoma *in situ* of the cervix, leading in previously cryptorchoid testes, to invasive carcinoma within 5 years in 70% (Skakkebaek and Berthelsen, 1978). In our patient this dangerous, potentially lethal condition was detected at an early stage by virtue of the endocrinological effects of a benign Leydig cell tumour.

Some 5.2% of patients with germ cell carcinoma *in situ* show similar changes in the contralateral testis (Berthelsen *et al.*, 1982). Unfortunately, our patient refused biopsy of the remaining left testis. We are therefore monitoring clinically and biochemically.

The precise nature of the pyrexial illness remains obscure but it is tempting to relate these symptoms to the presence of testicular neoplasia. Familial Mediterranean Fever is unlikely—there were no symptoms of abdominal pain or serositis and no family history of the condition. None of the known causes of a chronic intermittent pyrexia were identified, despite comprehensive investigation on several occasions when the patient was pyrexial. It is however of considerable interest that no pyrexial illness had occurred 14 weeks after orchidectomy. The neoplastic lesions might have secreted pyrogenic compounds,

but why this should have recurred every 4 to 6 weeks is not clear.

The endocrine changes we observed before surgery probably resulted from elevated oestradiol levels suppressing gonadotrophin release at hypothalamic level. Sub-normal FSH and LH concentrations, in combination with excess circulating and local oestradiol concentrations, could suppress both Leydig and germ cell activity resulting in low plasma testosterone levels and oligospermia.

Postoperatively, the LH response to LHRH was exaggerated suggesting relative Leydig cell insufficiency. Plasma oestradiol levels had decreased to within 1 pmol/litre of the reference range. The endocrine profile was otherwise normal postoperatively.

The histological appearance of the Leydig cell tumour accorded with previous descriptions (Gabrilove *et al.*, 1975; Shimpus *et al.*, 1977). Sheets of morphologically normal cells with acidophilic cytoplasm and round or slightly oval nuclei were seen, the cells in some instances exhibiting Reincke's crystals. Why morphologically normal cells should secrete increased quantities of oestrogen is not known. One suggestion is that aromatase activity is enhanced in such tumours, with consequent increased conversion of androgenic precursors to oestrogen, which in turn inhibits the activity of testosterone synthesizing enzymes, 17-hydroxylase and 17-20 lyase (Bercovic *et al.*, 1981).

The first noticeable clinical change after orchidectomy was a subtle alteration in behaviour. The patient became more assertive and less effeminate.

He was delighted at the absence of pyrexial attacks but somewhat displeased at the development of facial acne. Regression of gynaecomastia started 4 weeks post-operatively.

This case showed an unusual clinical presentation and dual pathology in the testis. For once 'double trouble' worked to the advantage of the patient, as his benign lesion drew attention to a dangerous pre-malignant condition.

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References

- BERCOVICI, J.P., TATER, D., SLEMEN, K., JEAN-FRANCOIS, C., FLOCH, J. & LEROY, J-P. (1981) Leydig cell tumour with gynaecomastia: hormonal effects of an oestrogen-producing tumour. *Journal of Clinical Endocrinology and Metabolism*, **53**, 1291.
- BERTHELSEN, J.G., SKAKKEBAK, N.S., MAASE, H. VON DER, SØRENSEN, B.L. & MOGENSEN, P. (1982) Screening for carcinoma in situ of the contralateral testis in patients with germinal testicular cancer. *British Medical Journal*, **285**, 1683.
- COLLINS, D.A. & PUGH, R.C.B. (1964) The pathology of testicular tumours. *British Journal of Urology*, **36**, (Suppl.) 42.
- DALGAARD, J.B. & HASSELBERG, F. (1957) Interstitial tumours of the testis. Two cases and survey. *Acta Pathologica et Microbiologia Scandinavica*, **41**, 219.
- DIXON, F.J. & MOORE, R.A. (1952) Tumours of the Male Sex Organs. In: *Atlas of Tumour Pathology*. Section 111. Fasc. 316 and 32. Washington D.C. Armed Forces, Institute of Pathology.
- GABRILOVE, J.L., NICOLIS, G.L., MITTY, H.A. & SOHVAL, A.R. (1975) Feminising interstitial cell tumour of the testis: personal observations and a review of the literature. *Cancer*, **35**, 1184.
- SHIMPIUS, W.S., SCHULTZ, A.L., HASTINGS, J.R. & ANDERSON, W.R. (1977) Leydig cell tumour of the testis with gynaecomastia and elevated oestrogen levels. *American Journal of Clinical Pathology*, **67**, 562.
- SKAKKEBAK, N.E. & BERTHELSEN, J.G. (1978) Carcinoma in situ of testis and orchiectomy. *Lancet*, **ii**, 204.

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