Virchows Arch (1997) 431:149–151

CASE REPORT

**Antonio López-Beltrán · Alfonso S. Calañas
Pilar Jimena · Alberto L. Escudero
Telma R. Campello · Manuel Muñoz-Torres
Fernando Escobar-Jiménez · Rafael E. Carvia
Francisco F. Nogales**

Virilizing mature ovarian cystic teratomas

Received: 8 January 1997 / Accepted: 28 February 1997

Abstract Three further cases of mature benign cystic teratomas of the ovary associated with virilization are added to the three previously reported in the literature. They were found in postmenopausal, obese, diabetic women aged 52, 61, and 67 years. The patients presented with hirsutism and voice changes and clitoromegaly was present in one. Testosterone and androstenedione levels were elevated but promptly regressed after removal of the tumours. Histologically, sheets of stromal luteinized cells were found peripherally at the interface between the neoplasm and ovarian tissue. Luteinization of ovarian stroma induced by an unknown factor related to diabetes mellitus is the origin of the virilization.

Key words Ovary · Androgen secretion · Cystic teratoma · Virilization · Luteinization

A. López-Beltrán · A.L. Escudero
Department of Pathology, Cordoba University Medical School and Reina Sofia University Hospital, Cordoba, Spain

A.S. Calañas
Department of Internal Medicine (Endocrinology), Cordoba University Medical School and Reina Sofia University Hospital, Cordoba, Spain

P. Jimena
Department of Gynaecology, Cordoba University Medical School and Reina Sofia University Hospital, Cordoba, Spain

R.E. Carvia · F.F. Nogales (✉)[1]
Department of Pathology, University Medical School, Granada, Spain

M. Muñoz-Torres · F. Escobar-Jiménez
Department of Endocrinology, University Medical School, Granada, Spain

T.R. Campello
Universidade Federal de Pernambuco, Brasil

Mailing address:
[1] Departamento de Anatomía Patológica, Facultad de Medicina, E-18012 Granada, Spain
Fax: (34) 58243510; E-mail: fnogales@goliat.ugr.es

Introduction

Many ovarian neoplasms of sex-cord stromal type, including tumours of hilus, Leydig, Sertoli-Leydig and lipid cell varieties, are associated with an excessive production of androgen [4, 5, 13]. In other ovarian tumours of epithelial, germ cell or metastatic origin, the neoplastic, non-steroidogenic cells may induce an abnormal sex steroidal secretory response in the ovarian stromal cells, which can occasionally be responsible for clinical manifestations of virilization [1, 2, 6, 12, 13]. The usual form of mature cystic teratoma of the ovary has been reported with virilization in three instances [1, 2, 12]. We present three further cases of this unusual clinicopathological combination.

Case Reports

Case 1

A 67-year-old woman complained of hirsutism, voice changes and parietotemporal balding for the last 6 years; she was obese with a body mass index (BMI) of 39.63 kg/m^2 and had controlled diabetes mellitus. Physical examination revealed evident clitoromegaly. On abdominal ultrasound and CT scan an 8×9 cm cystic mass was found in the right ovary. The patient underwent total hysterectomy with bilateral salpingo-oophorectomy (TAH-BSO).

Her testosterone levels were normal when measured 6 months after surgery.

Case 2

A 52-year-old woman was admitted with high blood pressure. On physical examination she was found to be obese (BMI: 36.7 kg/m^2), and she had diabetes mellitus. She was hirsute and had a hoarse voice. The abdominal ultrasound showed a 17.4×12.6 cm cystic tumour in the right ovary. The patient underwent a TAH-BSO. Six months after surgery, the testosterone level was normal.

Case 3

A 61-year-old woman presented with metrorrhagia. Clinical examination revealed an obese patient (BMI: 37.6 kg/m^2) with marked

Table 1 Preoperative hormonal data on three reported cases of ovarian teratoma showing peripheral stromal luteinization

Preoperative biomedical data	Case 1	Case 2	Case 3	Normal postmenopausal values
Oestradiol	61 pg/ml	7 pg/ml	6 pg/ml	<30 pg/ml
SHBG	44 nmol/l	36.9 nmol/l	–	30–100 nmol/l
Testosterone	4.5 ng/ml	3.1 ng/ml	4.5 ng/ml	0.3–1.2 ng/ml
Androstendione	2.7 ng/ml	2.3 ng/ml	2.1 ng/ml	0.36–1.8 ng/ml
DHEA-S	35 ng/dl	65.4 ng/dl	–	35–80 ng/dl
FSH	77.0 mUI/ml	26.6 mUI/ml	–	25–150 mUI/ml
LH	39.59 mUI/ml	6.9 mUI/ml	–	15–75 mUI/ml
17-OH-P	–	3.9 ng/ml	–	0.27–2.9 ng/ml
PRL	–	6.7 ng/ml	–	3.5–8.3 ng/ml
ACTH	–	9 pg/ml	–	7–77 pg/ml
Cortisol PL	–	30 µg/ml	–	5–20 µg/ml

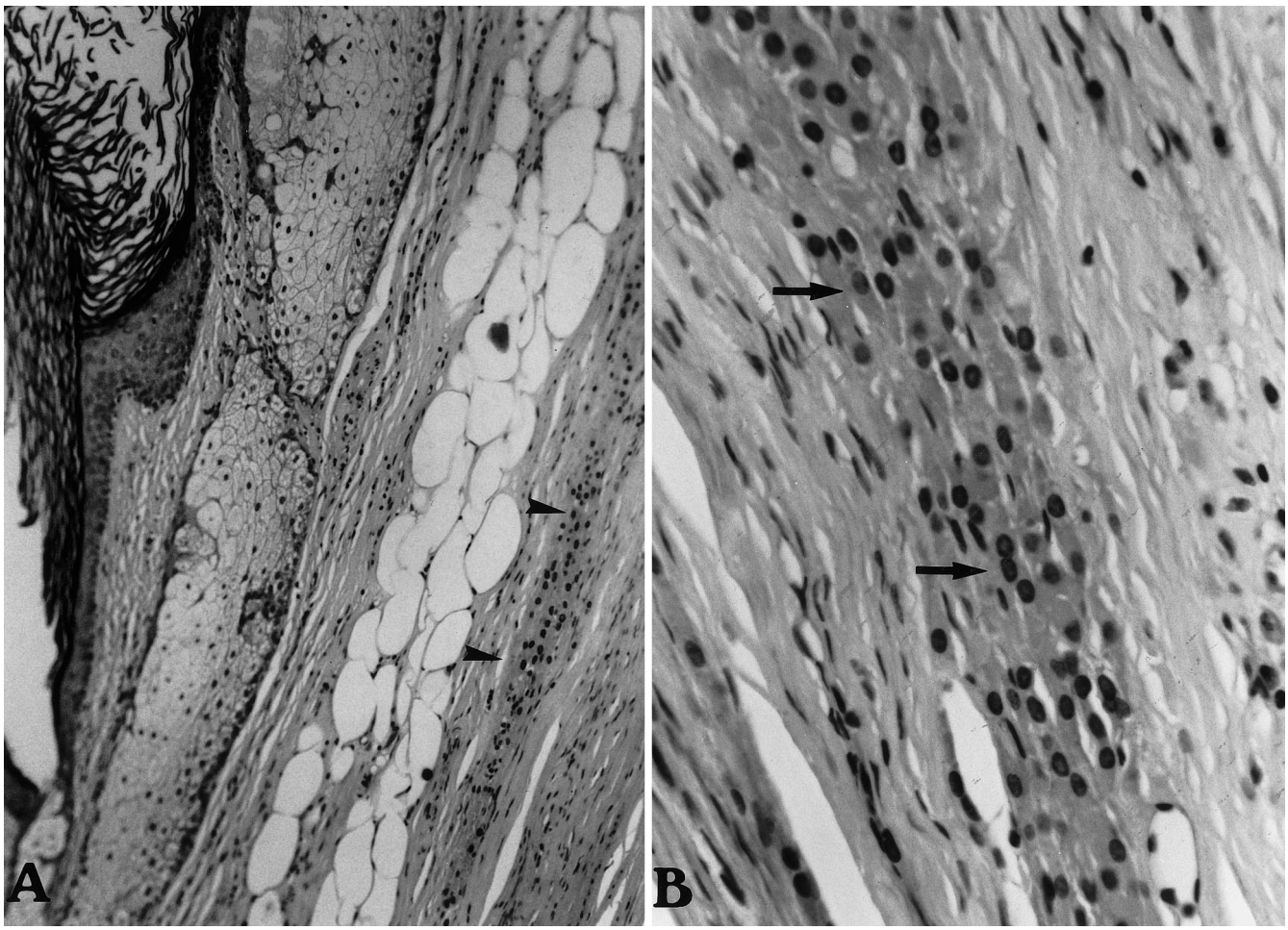

Fig. 1 **A** Low-power view of mature cystic teratoma showing stromal luteinized cells (*arrowheads*). **B** High-power view of stromal luteinized cells (*arrows*)

stigmata of hirsutism. She was also found to be diabetic. Abdominal ultrasound and CT scan revealed a cystic tumour of the right ovary, measuring 6.3×5 cm. She underwent a TAH-BSO. Six months after surgery the plasma testosterone was normal.

Detailed hormone values for the three cases are shown in Table 1.

Pathological findings

Microscopically, the mature cystic teratomas had the usual admixture of adult type tissues. At the interface between tumour and the surrounding ovarian tissue there were conspicuous bands or sheets of polygonal cells with an eosinophilic or clear vacuolated cytoplasm lacking Reinke´s crystalloids (Fig 1). The remaining ovarian tissue did not show any evidence of independent stromal hyperthecosis. The contralateral ovaries were unremarkable. Only in case 3 was the uterus abnormally enlarged, with endometrial changes of simple hyperplasia.

Discussion

Most germ cell tumours do not exhibit recognizable abnormalities of steroid hormone secretion [7, 13], and rapidly growing teratomas such as solid mature and the pure immature types have not shown steroid hormone abnormalities [13]. However, slow-growing mature teratomas and related varieties [13] have been associated with androgenic or oestrogenic manifestations on a number of occasions [1, 12, 13]. When functioning stroma is present in germ cell tumours, it is often found at the periphery and adjacent to the lesion rather than interspersed among the proliferating cells [13]. Five cases of struma ovarii and three further virilizing strumal carcinoids with peripheral luteinization have been recorded in the literature [3, 9, 10, 11, 12].

Only three cases of pure mature cystic teratomas showing peripheral luteinization associated with androgen excess have been reported in the English-language literature [1, 2, 12]. One of them was bilateral [1] and showed luteinized cells on both sides; regression of the manifestations of virilization followed surgical removal [8].

The three cases reported here had the usual histopathological features of mature cystic teratoma and had luteinized cells only at their periphery, at the interface between the mature teratoid tissues with the ovary. These cells, we believe, represented the principal source of both androstenedione and testosterone, since the hormonal levels returned to normal after the tumours were removed. Of the previously reported cases, with one had peripheral luteinization [2], another had hilus cell hyperplasia adjacent to the tumour [12] and in the remaining case [1] luteinization reflected a concurrent hyperthecosis rather than peripheral luteinization [13]. The three cases reported here are similar to the first one just mentioned [2], since the stromal luteinization was not of hilar type and the remaining ovarian stroma did not show stigmata of hyperthecosis.

Several explanations have been offered for the phenomenon of peripheral luteinization: one theory [14] proposes that the slow-growing tumour behaves in the same way as an enlarging follicle and that the pressure on the adjacent tissue induces the development of luteinized theca-like cells at the margins as they are pushed out. This explanation is most attractive for cases like ours.

Although the morphological features of stromal luteinization are clear, we do not know what stimuli may trigger the induction of luteinization in stromal cells at the menopause in an otherwise long-standing tumour that has (probably) been present since adolescence. It is noteworthy that all our cases occurred in postmenopausal, obese patients with non-insulin-dependent diabetes and the clinical profile was similar to that of endometrial carcinoma. This may indicate that extraovarian hormonal factors are responsible for this clinicopathological combination. We suggest that the usually elevated postmenopausal gonadotropin levels, together with the increased peripheral insulin resistance and hyperinsulinaemia of the type-2 diabetic patient, may act synergistically at the IGF-I receptor level, increasing androgen secretion by stromal cells [5].

References

1. Aiman J, Nalick RH, Jacobs A, et al (1977) The origin of androgen and estrogen in a virilized postmenopusal woman with bilateral benign cystic teratomas. Obstet Gynecol 49:695–704
2. Case Records of the Massachussetts General Hospital (1993) Case 24–1993. N Engl J Med 328:1770–1776
3. Dikman SH, Toker C (1971) Strumal carcinoid of the ovary with masculinization. Cancer 27:925–930
4. Honoré LH, Chari R, Mueller HD, Cumming DC, Scott JZ (1992) Postmenopausal hyperandrognism of ovarian origin: a clinicopathologic study of four cases. Gynecol Obstet Invest 34:52–56
5. Lobo RA (1991) Ovarian hyperandrogenism and androgen producing tumors. Endocrinol Metab Clin North Am 20:773–805
6. Moore JG, Schfrin BS, Erez S (1967) Ovarian tumors in infancy, childhood, and adolescence. Am J Obstet Gynecol 99:913–922
7. Nogales FF (1995) Germ cell tumours. In: Haines & Taylor's gynaecological and obstetrical pathology. Churchill Livingstone, London, pp 847–896
8. Norris HJ, Chorlton MB (1974) Functioning tumors of the ovary. Clin Obstet Gynecol 17:189–228
9. Okolo SO, Darley C, Melville HAH, Kirkham N (1990) Virilizing ovarian serous cystadenoma. Case report. Br J Obstet Gynaecol 97:269–271
10. Rooboy SJ, Scully RE (1980) Strumal carcinoma of the ovary: an analysis of 50 cases of a distinctive tumor composed of thyroid tissue and carcinoid. Cancer 46:2019–2034
11. Rosenfield RL, Lucky AW (1993) Acne, hirsutism and alopecia in adolescent girls. Endocrinol Metab Clin North Am 22:507–532
12. Rutgers JL, Scully RE (1986) Functioning ovarian tumors with peripheral steroid cell proliferation: a report of twenty-four cases. Int J Gynecol Pathol 5:319–337
13. Scully RE (1995) Ovarian tumors with functioning stroma. In Haines & Taylor´s gynaecological and obstetrical pathology. Churchill Livingstone, London, pp 983–996
14. Woodruff JD, Williams TJ, Goldberg B (1963) Hormone activity of the common ovarian neoplasm. Am J Obstet Gynecol 87:697–698