Upsala J Med Sci 110 (3): 233–236, 2005

Sertoli-Leydig Cell Tumour in a Postmenopausal Woman Showing all Facets of the Insulin Resistance Syndrome (IRS)

Eva Dahlgren [1], Berit Gull, Roger Willén [2], Frank Sundler [3], Thord Rosén [4] and Per-Anders Jansson [5]

[1]Department of Obstetrics and Gynecology the Sahlgrenska Academy at Göteborg University, [2]Department of Clinical Pathology and Cytology, Uppsala University Hospital, [3]Department of Physiological Sciences, Neuroendocrine Cell Biology, [4]University of Lund, Research Center for Endocrinology and Metabolism and [5]the Lundberg Laboratory for Diabetes Research the Sahlgrenska Academy at Göteborg University, Sweden.

ABSTRACT

Sertoli-Leydig cell tumours are rare sex stromal tumours with an incidence of <0.5% of all ovarian tumours. Most frequently this tumour occurs in young women with a history of amenorrhoea, hirsutism and lowered pitch. Here, we report on a woman with IRS, postmenopausal virilization and increased testosterone levels due to a Sertoli-Leydig cell tumour. This is the first case to suggest an association between IRS and Sertoli-Leydig cell tumours. Furthermore, we highlight the difficulties in detecting this ovarian tumour with sonography.

CASE REPORT

A 64-year-old woman with a three year history of hirsutism was referred to the Department of Ob&Gyn.

The woman is a IV-gravida, III-parous with regular periods until menopause at the age of 47. She smoked 15 cigarettes per day. In 1988, three years after menopause, she was diagnosed with and advised of lifestyle changes for central obesity and hyperlipidemia. In 1990 she was prescribed selective beta-blockade due to hypertension. In 1992 type 2 diabetes was diagnosed and she exhibited microalbuminuria, hence, the woman had developed an overt insulin resistance syndrome (IRS) (1). She became normoglycaemic after introduction of multiple insulin injection therapy.

However, diabetes complications appeared in the next few years. In 1995 mani-

Received 3 February 2004
Accepted 28 February 2005
Key words: Sertoli-Leydig cell tumour, Insulin resistance, Metabolic Syndrome, Exogenous Insulin treatment.

fest nephropathy and angina pectoris were diagnosed. In 1997, to improve metabolic control, normal insulin (Actrapid®) was substituted with insulin lispro (Humalolog®). Unfortunately, the woman reported worsening of her angina pectoris, and she was referred to the Cardiology unit. In 1998, she underwent a coronary artery by pass graft operation, involving five coronary vessels. Postoperatively, the woman reported no angina pectoris, quit smoking, and temporarily normalised her metabolic control.

Hirsutism was first noted in 1998 but worsened in early 2001. She reported daily cutting of facial hair. The endocrine investigation showed a total serum testosterone level that was markedly elevated (19 nmol/L). On suspicion of an ovarian origin for the high testosterone level a gynaecological examination and a vaginal ultrasound examination (Aloka SSD 2000) was performed with a normal finding.

An MR investigation of the adrenals excluded adrenal pathology and a second gynaecological ultrasound (ATL HDI 5000, vaginal probe 7.5 mHz) was performed. The left ovary measured 22x21x23 mm, was a little squared with some mixed echogenicity, but with normal, not increased circulation. The right ovary was found to be round with a diameter of 16 mm with no deviant echogenicity or vascularization. Thus, there was some suspicion of hypertrophy of the left ovary which led to a laparoscopic bilateral salpingoophorectomy of a normal left ovary and a right ovary enlarged to three times normal size, rounded, and without macroscopic evidence of tumorous vegetation on the surface. There were no signs of peritoneal carcinosis or ascites.

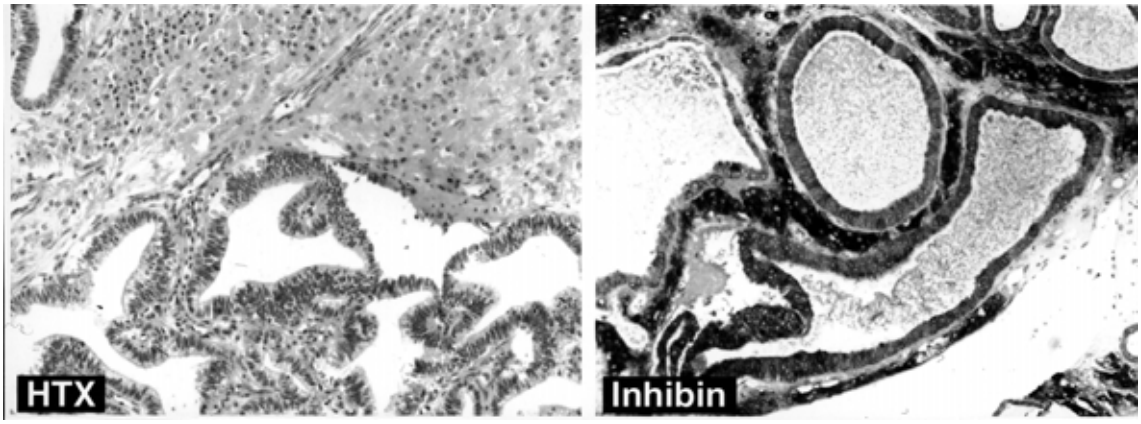

Fig 1: Overview of the Sertoli Leydig Cell Tumour, with Sertoli tubules at the bottom and clusters of Leydig cells at the top. Strong inhibin immunoreactivity in both Sertoli as well as in Leydig cell components. Magnification. x 120.

Histopathology confirmed a normal left ovary and in the right ovary an encapsulated well differentiated Sertoli-Leydig cell tumour, reaching 0.1 cm from the surface. The immuno-histochemical study showed a strong reaction for inhibin (Fig 1) In Sertoli-Leydig cell tumours inhibin is positive in 100% of cases. Tumour cells were

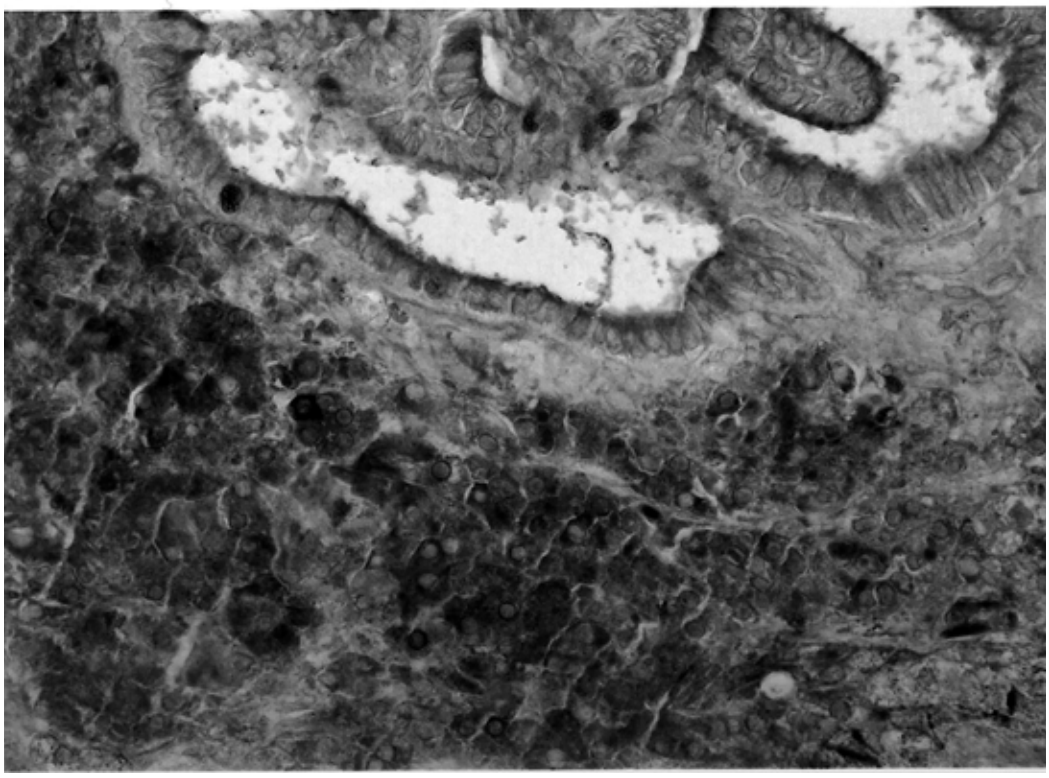

Fig 2: Diffuse slight positive immunohistochemical staining for insulin receptor within the Leydig cells but no staining of the Sertoli cells. Magnification. x 120.

IGF-1 receptor negative except for vessel walls. Furthermore, insulin receptor markers were negative on the Sertoli cells but diffusely slightly positive within the Leydig cells (Fig 2).

The testosterone level was normalised postoperatively (0.60 nmol/L). Metabolic control was not improved 6 months postoperatively, i e $HbA_1c \approx 9.0$ %.

DISCUSSION

This is the first time a Sertoli-Leydig cell tumour is described in a postmenopausal woman showing all characteristics of the IRS [1]. Our patient was treated with insulin as the initial therapy for her pronounced hyperglycaemia. Interestingly, chronic hyperinsulinaemia has been reported to cause an increased production of ovarian androgens including testosterone and a decrease in serum sex hormone-binding globulin [2], suggesting a link between IRS and hyperandrogenism.

Is it likely that hyperinsulinaemia caused the Sertoli-Leydig cell tumour in our patient? Since we did not find any impressive staining of insulin receptors in our tumour biopsies, which is in contrast to a previous report [3] one has to be cautious about any statement regarding an association between endogenous/exogenous hyperinsulinaemia and Sertoli-Leydig cell tumours based on this case report. How-

ever, it should be mentioned the solid theoretical background for the propensity to develop malignancies in subjects with the IRS [4-7]. Hence, it might be of value to consider this rare tumour in postmenopausal women exhibiting IRS and concomitantly receiving multiple injection therapy with high dosages of insulin to avoid hyperglycaemia.

The present case also highlights that false positive and false negative findings on ultrasonography of the ovaries may occur even in the hands of an experienced gynaecological ultrasonographer. Indeed, the opposite ovary, contrary to the sonographer's suggestion, was the site for the Sertoli-Leydig cell tumour. Therefore, to exclude a Sertoli-Leydig cell tumour, we recommend exploration with laparoscopy if the clinical picture implies a hyperandrogenic state, and ultrasound of the ovaries and MR of the adrenals both are normal.

REFERENCES

1. Alberti KGMM, Zimmet P for the WHO Consultation Group (1998). Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus. Diabet Med 15: 539-53.
2. Barbieri RL, Smith S, Ryan KJ (1998). The role of hyperinsulinaemia in the pathogenesis of ovarian hyperandrogenism. Fertil Steril 50: 197-212.
3. Nagamani M, Stuart CA, Van Dinh T (1989). Steroid biosynthesis in the Sertoli-Leydig cell tumour: effects of insulin and luteinizing hormone. Am J Obstet Gynecol 161: 1738-43.
4. Stoll BA (2002). Upper abdominal obesity, insulin resistance and breast cancer risk. Int J Obes Relat Metab Disord 26: 747-53.
5. Colangelu LA, Gapstur SM, Gann PH, Dyer AR, Liu K (2002). Colorectal cancer mortality and factors related to the insulin resistance syndrome. Cancer Epidemiol Biomarkers Prev 11:385-91.
6. Hsing AW, Gao YT, Chua S Jr, Deng J, Stanczyk FZ (2003). Insulin resistance and prostate cancer risk. J Natl Cancer Inst 95: 67-71.
7. Kurtzhals P, Schaffer L, Sorensen A, Kristensen C, Jonassen I, Schmid C, Trub T (2000). Correlations of receptor binding and metabolic and mitogenic potencies of insulin analogs designed for clinical use. Diabetes 49: 999-1000

Corresponding author: Eva Dahlgren MD, PhD
Department of Obstetrics and Gynecology
SU Sahlgrenska
435 14 Gothenburg
Sweden
Phone:+46313421000
E-mail:eva.dahlgren@vgregion.se