A rare ovarian Leydig cell tumor (hilar type) causing virilization in a postmenopausal woman

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Summary

All patients with virilization signs, increased levels of androgen hormones and rapidly progressive hirsutism should be evaluated for an androgen-producing tumor. The ovarian origin of virilization can be suspected by the presence of elevated levels of circulating androgens, with normal levels of cortisol metabolites and a negative dexamethasone suppression test. A case report of a 50-year-old postmenopausal patient with rapidly progressive hirsutism is presented. After an extensive preoperative investigation a right oophorectomy was performed and a Leydig-hilus cell tumor was diagnosed.

Key words: Hilus-cell tumor; Leydig-cell tumor; Sex cord-stromal tumors; Ovary; Virilization.

Introduction

Leydig cell neoplasms are rare sex cord-stromal ovarian tumors of postmenopausal women, that represent 0.1% of all ovarian tumors and 20% of steroidogenic cell tumors of the ovaries [1-3]. It is important to distinguish these tumors that are benign from the otherwise non specified steroid cell tumors, which present similarities in morphology but occur in younger women and present malignant behavior in about 20-45% of the reported cases.

Case Report

A 50-year-old postmenopausal white woman, gravida 2, para 1, was admitted to our hospital for evaluation of hirsutism. From her past medical history, a sigmoidectomy was reported because of a well differentiated adenocarcinoma (Stage 1) with negative lymph nodes. The patient has been free from neoplastic disease for the last three years but has reported progressive facial hirsutism for the last two years as well as an advanced stage of acne and weight increase. No evidence of breast flattening or change in libido has been noted.

The initial physical examination revealed signs of virilization such as facial hair (beard) and male distribution of pubic hair. The gynecological examination disclosed a normal uterus; the clitoris was enlarged but no pelvic mass was palpable. Her weight was 93 kg, height 164 cm, and body mass index (BMI) 34.58.

Measurements of circulating hormones revealed increased levels of testosterone. Androstenedione, dehydroepiandrosterone (DHEAS) and cortisol metabolites were within normal range. Cushing's syndrome was ruled out by an overnight dexamethasone suppression test. An abdominal computed tomography (CT) scan and pelvic ultrasound (US) showed no tumor mass in the andrenal glands. Transvaginal ultrasound (TVS) of the ovaries showed a cystic enlargement of the right ovary that measured 5 cm in mean dimension. A right oophorectomy was performed and frozen section examination was negative for malignancy.

On macroscopic examination the right ovary measured 5 x 2.3 x 1.8 cm, and the cut section revealed cysts with a diameter of 0.5-2 cm. After formalin fixation of the specimen, semiserial sections were stained with hematoxylin-eosin. Microscopic examination of the ovary revealed a circumscribed neoplasm brown in color, measuring 2 cm, containing a cystic hemorrhagic area measuring 1 cm at the ovarian hilus (Figure 1). It was composed of large uniform polyhedral cells characterized by spherical vesicular nuclei containing one to two nucleoli, and granular cytoplasm (Figure 2). Adjacent ovarian tissue showed hilus cell clusters and stromal hyperplasia. Although no Reinke crystalloids were observed in the multiple sections examined, the overall pathological diagnosis was that of a Leydig (hilus) cell tumor of the right ovary. After two months the circulating hormones of the patient were within normal levels and the facial and body hair had disappeared.

Discussion

In a postmenopausal woman mild hirsutism is generally idiopathic and the hormonal screening is frequently normal. However, a patient with virilization, increased levels of androgen hormones and rapidly progressive hirsutism should be evaluated for an androgen-producing tumor. The adrenal glands and ovaries should be examined. The ovarian origin of virilization can be suspected by the presence of elevated levels of circulating androgens, with normal levels of cortisol metabolites and a negative dexamethasone suppression test.

The majority of hormone producing ovarian tumors are derived from specific stromal and sex cord cells of the ovary. Steroid cell tumors account for approximately 0.1% and are composed of large round or polyhedral cells that resemble lutein, Leydig and adrenocortical cells. In the past, the term lipoid or lipid cell tumors has been used but currently the term *steroid cell tumors* is generally accepted. The new term was proposed because 25% of the tumors do not contain intracellular fat. Steroid cell

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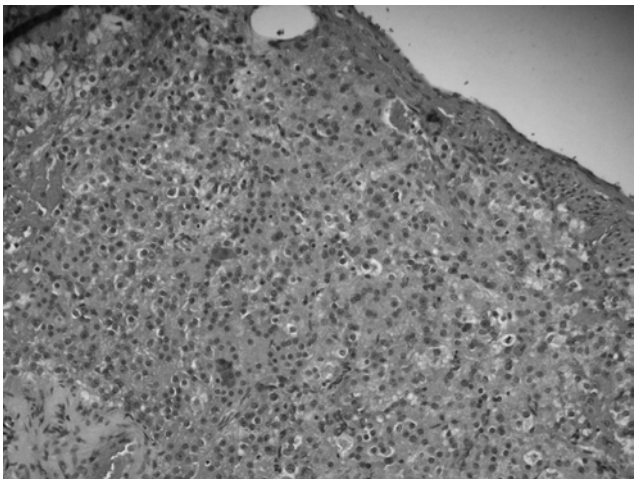

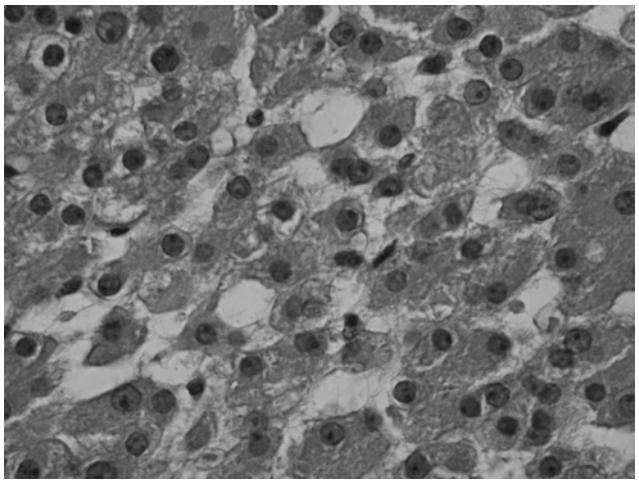

Figure 1. — Histological section of a hilus cell tumor of the ovary (H&E x 100).
Figure 2. — Histological section of a hilus cell tumor consisting of large uniform cells with spherical nuclei containing one or two nucleoli (H&E x 250).

tumors are divided into three major categories: a) stromal luteoma, b) Leydig cell tumors, and c) steroid cell tumors not otherwise specified. Leydig cell tumors are divided into three subgroups i) Hilus cell tumors, ii) Leydig cell tumors, non-hilar type, iii) Leydig cell tumors, not otherwise specified. Steroid cell tumors not otherwise specified have two subgroups i) well differentiated and ii) malignant [1]. Hilus cell tumors of the ovaries are rare tumors representing only 0.1% of all ovarian tumors, and arise from specific cells in the ovarian hilus, called hilus cells. These tumors are almost unilateral but in the literature four cases of bilateral hilus cell tumors have been reported [2, 4, 5]. Hilus cell tumors typically occur in postmenopausal women at a mean age of 58 years, but occasionally they may be detected in pregnant women or children [2, 4]. These tumors are frequently the cause of increased circulating levels of androgenic hormones, but estrogenic effects as polyps, endometrial hyperplasia and adenocarcinomas have been reported as well [2, 3]. In 80% of patients, hilus cell tumors cause hirsutism or virilization as in our patient [6, 7]. The physical examination may reveal facial hair, masculine alopecia and male distribution of pubic hair, seborrhoeic skin and acne as well as atrophy of the breast and enlargement of the clitoris. Hypertension, diabetes, and Cushing's syndrome have also been described [2]. In the literature hilus cell tumors have also been associated with polycystic ovarian syndrome and thyrotoxicosis [2]. The ovarian origin of the hirsutism in the current study was suspected by the presence of elevated levels of circulating androgens, with normal levels of cortisol metabolites and a negative dexamethasone suppression test. The first radiological studies for diagnosis of ovarian and adrenal tumors are CT scan and TVS. Imaging studies in this case did not detect any obvious mass of the andrenal glands or ovaries. TVS revealed an enlargement of the right ovary (5 cm), as found in the 96% of hilus tumors reported by other authors [8]. During the first five years after menopause, ovaries atrophy to a mean volume of 4.0 ± 1.8 cm, and TVS is particularly useful to estimate the ovarian volume and detect possible cancerous conditions. Recently the suppression of androgen levels with GnRH analogues has been described as a diagnostic method [2, 3]. These methods are non invasive, sensitive and widely available. Only by histological examination can a definitive diagnosis be established.

Macroscopically hilus cell tumors are typically small (less than 5-6 cm), and usually well circumscribed or lobular with a reddish brown to yellow appearance on sectioning and rarely bilateral [5]. In our case the tumor was circumscribed and partly cystic on cut section. Hilus (Leydig) cell tumors originate from normal hilus cells present in the ovarian hilus and the mesovarium. These tumors are composed of uniform large or polyhedral cells and a spherical, eccentrically placed vesicular nucleus with one or more nucleoli arranged in sheets, cords or nests. The cytoplasm may contain inclusion of lipids and lipochrom pigment may be seen in varying numbers of tumor cells. Although the presence of Reinke crystalloids is considered pathognomonic, in our case, in multiple histological sections, they were undetectable. In the literature crystalloids are described in only 50% of reported tumors [3, 9] and in any case, the detection of crystalloids may require a thorough histological search. Hilus cell tumors are considered as benign and so far only two malignant cases have been reported in the literature [3]. In our case, because of the presence of an enlarged right ovary, the rapid progression of hirsutism and the increased levels of testosterone the patient underwent right oophorectomy. Surgical removal is generally required for effective treatment of virilizing tumors, either laparoscopically or by laparotomy [2, 8, 10]. Hysterectomy is not considered necessary because of the benign biological behavior of the hilus cell tumors [2].

In conclusion hilus cell tumors are rare ovarian hormonally active tumors and should be suspected in post-

menopausal women with rapid progressive virilization and normal cortisol levels, even in cases where they are difficult to detect by imaging techniques due to their small size.

References

[1] Tavassoli F.A., Devilee P.: "Tumors of the ovary and peritoneum". World Health Organization classification of tumours: Pathology and genetics of tumours of the breast and female genital organs". UK, Oxford University Press, 2003

[2] Baiocchi G., Manci N., Angeletti G., Celleno R. Fratini D., Gilardi G.: "Pure Leydig cell tumour (hilus cell) of the ovary: a rare cause of virilization after menopause". *Gynecol. Obstet. Invest.*, 1997, *44,* 141.

[3] Zafrakas M., Vanizelos I.D., Theodoridis T.D., Zepiridis L., Agorastos T., Bontis J.N.: "Virilizing ovarian hilus (Leydig) cell tumor with concurrent contralateral hilis cell hyperplasia: a rare diagnosis". *Eur. J. Gynaecol. Oncol.*, 2009, *30*, 330.

[4] Silva P.D., Sorensen M.L., Reynertson R., Virata R.L., Mahairas G.H.: "Laparoscopic removal of virilizing hilar cell tumor in a postmenopausal patient". *J. Am. Assoc. Gynecol. Laparosc.,* 1997, *4,* 499.

[5] Duun S.: "Bilateral virilizing hilus (Leydig) cell tumors of the ovary". *Acta Obstet. Gynecol. Scand.,* 1994, *73,* 76.

[6] Mclellan A.R., Mowat A., Cordiner J.: "Hilus cell pathology and hirsutism". *Clin. Endocrinol.,* 1990, *32*, 203.

[7] McLellan A.R., Mowat A., Cordiner J., Beastall G.H., Wallace A.M., Connell J.M., Davies D.L.: "Hilus cell pathology and hirsutism". *Clin. Endocrinol. (Oxf.),* 1990, *32,* 203.

[8] Picón M.J., Lara J.I. , Sarasa J.L., Recasens J.D., Clouet R., Gonzalo M.A., Rovira A.: "Use of a long-acting gonadotrophin-releasing hormone analogue in a postmenopausal woman with hyperandrogenism due to a hilus cell tumor". *Eur. J. Endocr.,* 2000, *142,* 619.

[9] Paraskevas M., Scully R.E.: "Hilus cell tumors of the ovary. A clinicopathological analysis of 12 Reinke crystal-positive and nine crystal-negative cases". *Int. J. Gynecol. Pathol.,* 1989, *8,* 299.

[10] Sternberg W.H., Roth L.M.: "Ovarian stromal tumor containing Leydig cells. Stromal-Leydig cell tumor and non-neoplastic transformation of ovarian stroma to Leydig cells". *Cancer,* 1973, *32,* 940.

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