

# Virilizing ovarian hilus (Leydig) cell tumor with concurrent contralateral hilus cell hyperplasia: a rare diagnosis

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## Summary

Ovarian hilus or Leydig cell tumor and ovarian hilus cell hyperplasia are rare clinical entities, causing virilization in both pre- and postmenopausal women. Differentiation between these two conditions is not always straightforward; the former is usually unilateral appearing as a single, grossly visible, circumscribed mass of hilus cells, while the latter is usually bilateral, appearing as diffuse microscopic aggregates of hilus cells. We report herein an extremely rare case of ovarian hilus or Leydig cell tumor, presenting concurrently with contralateral ovarian hilus cell hyperplasia in a postmenopausal woman with virilization. To the best of our knowledge, only four such cases have been previously reported in the literature. Ovarian hilus cell tumors and hilus hyperplasia almost always have benign biological behavior, thus making bilateral salpingo-oophorectomy an appropriate and sufficient therapeutic approach.

**Key words:** Ovarian Leydig cell tumor; Ovarian hilus cell tumor; Ovarian hilus cell hyperplasia; Virilization; Ovarian tumor.

## Introduction

Virilization in postmenopausal women is a rare clinical condition. The underlying cause in such cases is hyperandrogenemia due to androgen over-production in either the adrenal glands or the ovaries. Ovarian Leydig or hilus cell tumor is a rare cause of postmenopausal virilization [1]. An extremely rare case of ovarian Leydig or hilus cell tumor presenting concurrently with contralateral ovarian hilus cell hyperplasia in a postmenopausal woman with virilization is reported.

## Case Report

A 55-year-old white female, G2, P2, was referred to our Department, due to partial scalp alopecia and facial hirsutism. On admission, physical examination revealed increased hair growth on the patient's breasts, back and extremities, while mild clitoris enlargement was noted. There was no palpable ovarian tumor on pelvic examination, and no abnormal findings on transvaginal ultrasound scan. Measurement of circulating hormones showed increased levels of testosterone, while androstenedione and dehydroepiandrosterone (DHEAS) were normal. In contrast, cortisol metabolites were within the normal range, and Cushing's syndrome was ruled out by an overnight dexamethasone suppression test. Magnetic resonance imaging (MRI) of the head showed a normal pituitary gland. Computed tomography (CT) of the upper and lower abdomen did not show any pathological signs; particularly both adrenal glands appeared normal. Subsequently, the patient underwent an exploratory laparotomy with bilateral salpingo-oophorectomy due to the presumptive diagnosis of virilization of ovarian origin. On macroscopic examination, a well circumscribed, 2-cm,

rubbery, yellowish-orange tumor was found in the left ovary; there were no abnormal macroscopic findings in the contralateral gonad. Microscopically, the well-circumscribed tumor of the left ovary consisted of polyhedral cells almost identical to normal hilus cells, infiltrating the adjacent ovarian stroma and vascular spaces (Figure 1). Interestingly, microscopic examination of the right ovary also showed foci of Leydig cells infiltrating the adjacent ovarian stroma and vascular spaces, a growth pattern consistent with hilus cell hyperplasia (Figure 2). No components of Sertoli cell tumor were observed. Immunohistochemical analysis showed that Leydig cells in both ovaries were positive for  $\alpha$ -inhibin (Figure 3) and vimentin, findings consistent with morphological diagnosis, and negative for pancytokeratin (AE1/AE3), epithelial membrane antigen (EMA), CD68, desmin and smooth muscle actin (SMA), findings excluding epithelial or muscular origin [3]. Testosterone

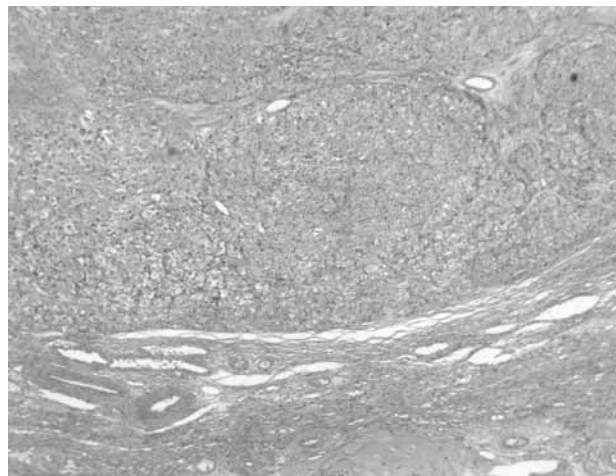


Figure 1. — Microscopic section of the left ovary showing hilus (Leydig) cells infiltrating the adjacent ovarian stroma and vascular spaces (H&E x 100).

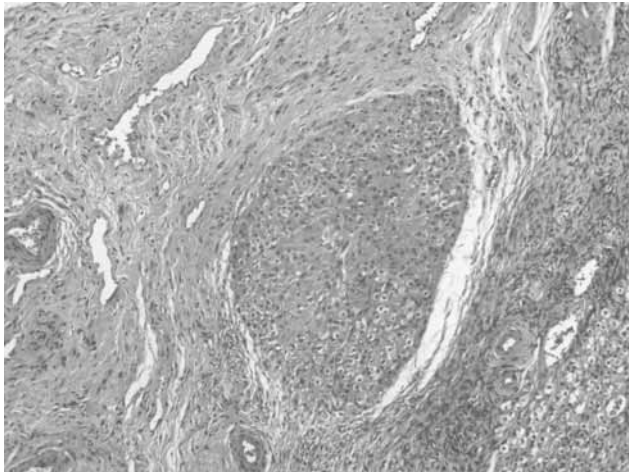


Fig. 2

Figure 2. — Microscopic section of the right ovary showing foci of hilus (Leydig) cells, a growth pattern consistent with hilus cell hyperplasia (H&E x 100).

Figure 3. — Immunohistochemical staining for  $\alpha$ -inhibin with positive neoplastic cells.

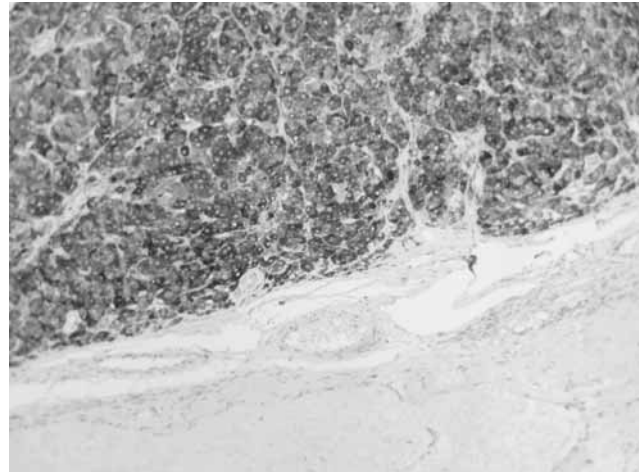


Fig. 3

levels were measured one month postoperatively and were found to be normal. No additional therapy was given to the patient postoperatively, and two years later she was still doing well, with no signs of tumor or virilization recurrence.

## Discussion

Ovarian hilus or Leydig cell tumor is a rare clinical entity, causing virilization in both pre- and postmenopausal women. These tumors consist of hilus cells which are normally found in the hilus of most normal ovaries and are morphologically identical to testicular Leydig cells [1, 3]. In this report an extremely rare case of a unilateral ovarian hilus cell tumor with concurrent hilus cell hyperplasia in the contralateral ovary is presented. To the best of our knowledge, only four such cases have been previously reported in the literature [1, 4]. It should be noted, that bilateral hilus cell tumors are also rare, with only four reported cases [3, 4-7].

Differentiation between hilus cell tumor and hilus cell hyperplasia on histologic examination can sometimes be difficult; a single, grossly visible, circumscribed mass of hilus cells is usually characterized as an adenoma or a tumor, while diffuse microscopic collections or aggregates of hilus cells are usually called hyperplasia [3,8]. Both pathologic entities may cause androgen overproduction and virilization. Ovarian hilus cell tumors are usually unilateral, while hyperplasia usually affects both ovaries [3], and is sometimes found lining the wall of ovarian cysts [8,9].

Ovarian Leydig cell tumors should not be confused with ovarian Sertoli-Leydig tumors, which may also cause clinical virilization in 70-85% of patients [10, 11]. Normally, there are no Sertoli cells in the adult ovary, while Leydig-like cells are usually seen in the hilus – in at least 83% – of normal female gonads [1, 3, 10]. It has been suggested that in Sertoli-Leydig cell tumors, cells of the sex cord differentiate into Sertoli cells, while Leydig cells originate from normal cells of the hilus [10-12].

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. Suppression of androgen levels after administration of GnRH analogues and exogenous estrogens has been described as part of the diagnostic work-up of these tumors [13, 14], but histological examination is the only way to establish a definitive diagnosis. Co-existence of hilus cell tumors with a normal pregnancy [1, 15, 16], other ovarian tumors [17] as well as pathologic conditions of the endometrium, including polyps, hyperplasia, and carcinoma [1, 18, 19], has been previously reported.

The therapeutic management of ovarian hilus cell tumors and hilus hyperplasia is primarily operative, consisting of bilateral salpingo-oophorectomy, either laparoscopically [20, 21] or with a classical open procedure. Since these tumors almost always have benign biological behavior [1], hysterectomy is not usually necessary. After oophorectomy androgen levels usually rapidly return to the normal range, and virilization subsides progressively to a varying extent thereafter [8].

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