CASE REPORT

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Ethics statement

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Pure Leydig cell tumor of the ovary in a premenopausal woman

Tumor de células de Leydig puro de ovario en mujer premenopáusica

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ABSTRACT

Leydig cell tumors of the ovary are a rare type of sex cord-stromal tumors, corresponding to less than 0.1% of all ovarian neoplasms. With a low incidence and frequent false-negative imaging results, these tumors represent a diagnostic challenge. Although more common in menopause, cases have also been described in premenopausal women. The most common clinical feature is rapidly progressive virilization; over 75% of patients show signs of virilization due to testosterone overproduction. Serum testosterone concentration is the most useful marker for diagnosing androgen-secreting tumors of the ovary. Leydig cell tumors should always be considered in women of reproductive age with virilization symptoms. We present the case of a pure Leydig cell tumor of the ovary in a premenopausal woman.

Key words: Leydig cell tumor, Ovarian neoplasms, Virilization.

RESUMEN

Los tumores de células de Leydig del ovario son un tipo raro de tumores del estroma del cordón sexual, con menos de 0,1% de todos los tumores de ovario. Representan un desafío diagnóstico, no solo por su incidencia esporádica sino también por presentar imágenes aparentemente normales. Aunque son más comunes en las mujeres menopaúsicas, también se ha descrito casos en mujeres premenopáusicas. La característica clínica más común es la aparición de virilización rápida y progresiva; más de 75% de las pacientes muestra signos de virilización debido a la sobreproducción de testosterona. La concentración sérica de testosterona representa el marcador más útil en el diagnóstico del tumor ovárico secretor de andrógenos. El tumor de células de Leydig ovárico siempre debe ser considerado en mujer en edad reproductiva con síntomas de virilización. Se presenta un caso de tumor de células de Leydig puro de ovario en mujer premenopáusica.

Palabras clave. Tumor de células de Leydig, Neoplasias de ovario, Virilismo.

Introduction

Leydig cell tumors derive from stromal cells of the ovarian sex cord. This uncommon malignancy accounts for 0,1% of all ovarian tumors, which are a rare cause of hyperandrogenism[1-3]. Leydig cell tumors appear most frequently in menopausal, and rarely in premenopausal women. Their most important clinical feature is fast and progressive virilization due to the excessive non-regulated production of testosterone[3,4]. They frequently have a benign behavior, an excellent prognosis and symptom reversal after surgical treatment[4]. We present the case of a pure Leydig cell tumor of the ovary in a premenopausal woman.

Case report

A 42-year-old patient, gravida 2, para 2, presented for rapid onset of hyperandrogenism characterized by increased facial hirsutism and frontal baldness over the last 6 months, without changes in voice tone. Patient's menarche was at age 14; she had regular periods until amenorrhea ensued 5 years ago, which was considered to be associated to polycystic ovarian syndrome. She had a history of hypothyroidism, non-insulin-dependent diabetes, class II obesity and obstructive sleep apnea. She denied taking oral contraceptives or androgenic drugs, smoking, drinking alcohol, endocrine disease and any relevant personal or family history.

At physical examination, the patient had no fever, heart rate of 90 beats per minute, blood pressure of 140/85 mmHg, and body mass index of 29 kg/m2. We observed the following clinical signs of hyperandrogenism: hirsutism in face, chest, upper limbs, anterior abdominal wall and lower limbs (Ferriman-Gallwey score of 20 points), androgenic frontal alopecia (Ludwig scale grade IV); no acne. Thyroid examination was normal. Abdomen was soft and depressible, painless, without visceromegaly or striae; there was no acanthosis nigricans. Pelvic examination revealed normal clitoral size, without any palpable pelvic tumors. We found no clinical characteristics of Cushing syndrome or any other endocrine pathology. The rest of the physical examination was normal.

Laboratory tests revealed elevated total testosterone in serum (1 367 ng/dL, reference value (RV) 14 to 76 ng/dL). The following tests had normal results: estradiol (40.6 pg/mL, RV <5 to 54.7 pg/mL), androstenedione (1.5 ng/mL, RV 0.3 to 2.99 ng/mL), dehydroepiandrosterone sulfate (68 µg/dL, RV 12 to 154 µg/dL), sex hormone-binding globulin (32 nmol(L, RV 9.3 to 100 nmol/L), urinary free cortisol (20 µg/24 hours, RV 20 to 137 µg/24 hours), thyroid-stimulating hormone (1.8 mUI/mL, RV 0.3 to 4.2 mUI/mL), 17-hydroxyprogesterone (2.0 ng/dL, RV 0.11 to 1.20 ng/mL) and prolactin (5.4 ng/mL, RV 1.2 to 29.9 ng/mL). Gonadotropin levels were low (luteinizing hormone 0.2 mUI/mL, RV 10.4 to 64.4 mUI/mL and follicle-stimulating hormone 0.2 mUI/mL, RV 25.8 to 150.3 mUI/mL). Liver and renal function tests, coagulation profile and serum glucose levels were also within normal limits. Alpha-fetoprotein, CA 19.9, CA-125 and chorionic gonadotropin levels were within the reference range. Urinary 17-ketosteroids and 17-hydroxycorticosteroids levels were normal. Dexamethasone suppression test (0.75 mg 4 times a day for 5 consecutive days) yielded suppressed cortisol values that did not affect total testosterone levels (905 ng/dL), suggesting a possible ovarian origin. Both adrenal glands were average size on ultrasound. Chest and abdominal x-rays and electrocardiogram showed no alterations.

Suspecting hyperandrogenism of ovarian etiology, we prescribed a pelvis MRI, which detected a tumor in the left ovary measuring 34 mm in diameter (Figure 1). Both adrenal glands were normal and there was no ascites nor pelvic or paraaortic lymphadenopathies. Given these findings, we performed laparoscopic surgery. Direct observation revealed a slightly bigger left ovary presenting a solid yellow-brown nodule, which prompted us to perform oophorectomy. We did not find ascites nor peritoneal lesions. The patient evolved favorably and was discharged 4 days after surgery.

Histopathologic examination reported the left ovary measured 27 x 22 x 17 mm and presented gray surface and irregular yellow-brownish areas in hilum measuring 17 mm in diameter, with capsule intact. At microscopy, cells were small, polygonal and uniform, with a pale, eosinophilic cytoplasm, a considerable amount of well-delimited lipoid matter, and small nuclei with peripheral dark chromatin, containing one or two prominent nucleoli (Figures 2 and 3). Cells were arranged in nests and irregular cords, surrounded by fibrotic and hyaline stroma. There was no cellular atypia, mitotic figures or evidence of necrosis. Nevertheless, there were abundant Reinke crystals. Tumor cells stained positive for inhibin A, calretinin, pancytokeratin and luteinizing hormone receptor, all markers for Leydig cells, and negative for chromogranin A, smooth muscle actin and SOX-9 – markers for Sertoli cells. These findings were consistent with Leydig cell tumor of the ovary without signs of malignancy.

One month after surgery, total testosterone levels were below 3 ng/dL. Follicle-stimulating and luteinizing hormone levels were within normal

Figure 1. Axial image of T2-weighted MRI. The arrow points to the ovarian tumor.

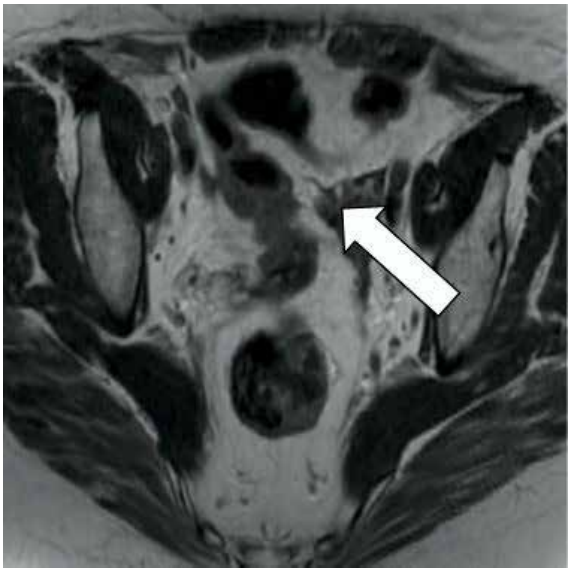


Figura 2. Histology image of A) well circumscribed Leydig tumor with B) normal adjacent ovarian tissue.

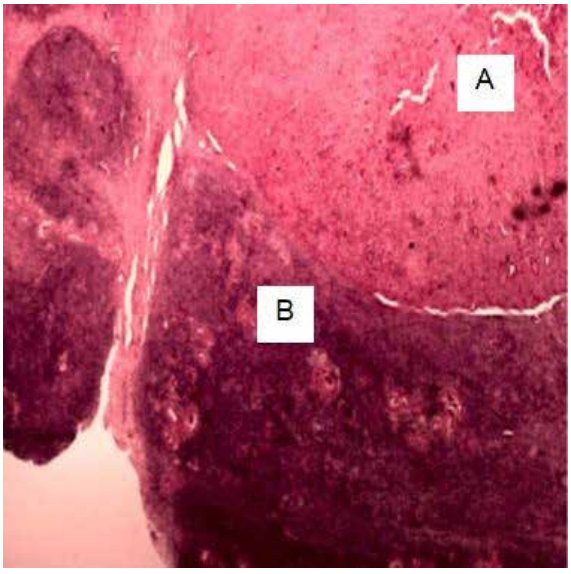
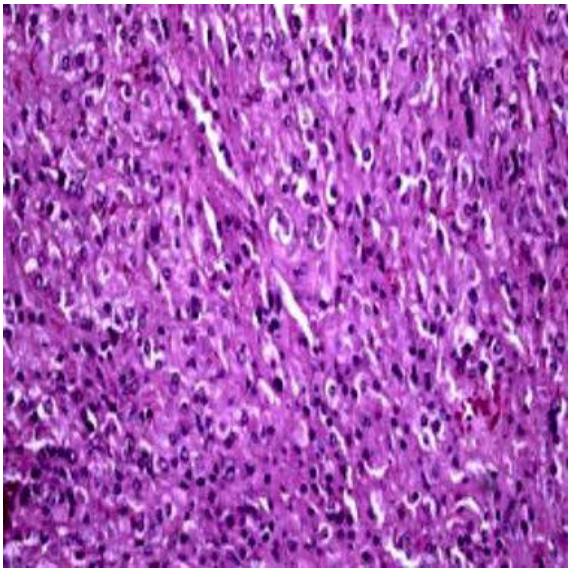


Figure 3. Microscopic image of Leydig cell tumor of the ovary presenting polygonal cells with ample eosinophilic cytoplasm and round, regular nuclei.



limits (7.3 mUI/mL and 15.2 mUI/mL, respectively). Six months after surgery, testosterone levels remained within the reference range and we observed milder hirsutism (Ferriman-Gallwey scale 6 points) and stabilization of alopecia.

Discussion

Sex cord-stromal tumors are the most common androgen-secreting ovarian tumors and represent less than 0,5% of all ovarian cancers. 15 to 20% of these tumors are Leydig cell tumors[5]. Leydig cell tumor can be derived from ovarian hilar cells, so they are considered the ovarian equivalents of Leydig testicular cells. It can also develop initially from the ovarian stroma. Therefore, ovarian Leydig cell tumors can be subdivided into hilar and non-hilar. In most cases, they are composed of polyhedral to rounded cells with generally abundant eosinophilic cytoplasm. Lipid vacuoles inside the cytoplasm may be present with or without lipofuscin pigment and tumor cells may contain Reinke crystals[6]. This type of ovarian tumor, mostly benign, has been found mainly in menopausal women between ages 50 and 70, with only a few cases in premenopausal women[7,8]. Pathogenesis of Leydig cells proliferation and tumor growth remains unclear, although the most accepted hypothesis is that it could develop autonomously or by central stimulation[2].

In women with rapid virilization, clinical history and detailed physical examination are critical to obtain a precise diagnosis. Clinical features of hyperandrogenism are affected by age at presentation, hormonal activity and virilising properties of the tumor. Patients may present various symptoms, including pain or abdominal bloating. However, the most common clinical presentation is associated to hormonal activity with virilising effects (75% of cases), such as severe hirsutism, frontal alopecia, clitoromegaly, increased libido, altered body fat distribution, increased muscle mass, mammary atrophy, deepening of the voice and pustular acne. Symptoms appear 5 to 7 years before diagnosis[8-10]. Usually, virilization has two defined phases: early “defeminization” (loss of female secondary sex characteristics) and “masculinization”. Usually, the first manifestation in a premenopausal woman with normal menstrual cycles is oligomenorrhea or amenorrhea, followed by mammary gland and external genitalia regression, and uterine and appendage atrophy. Afterwards, hirsutism, alopecia, acne, clitoromegaly, increased libido and sterility may arise[11,12].

Hyperandrogenism, especially virilization in premenopausal women, is a common finding, generally caused by polycystic ovarian syndrome or other conditions, resulting in a challenging diagnosis. Other possible causes for excessive androgen production include adrenal hyperplasia, adenoma and carcinoma, rare ovarian tumors (Sertoli-Leydig cell tumor of the ovary, dysgerminoma, gonadoblastoma, lipid cell tumor), Cushing syndrome, partial congenital adrenal hyperplasia and iatrogenesis, such as drugs[2]. Leydig cell

tumors are generally small (below 50 mm in diameter), slightly bigger than a normal ovary and yellow, orange or, more frequently, brownish [13].

Clinical signs of virilization must be confirmed by hormone testing. Women normally produce 0.1 to 0.4 mg of testosterone per day; 25% is secreted by ovaries, 25% by adrenal glands and the remaining 50% is a product of peripheral metabolism of hormones[2]. Serum testosterone levels over 200 ng/dL would confirm an androgen-producing tumor. Dehydroepiandrosterone sulfate levels below 600 mg/dL exclude an adrenal origin. In some cases, elevated estradiol levels may be due to testosterone aromatization[1]. Given the limitations of serum testosterone levels for identifying virilising tumors, we can obtain a more accurate diagnosis of androgen-producing tumors by characterizing the changes in testosterone levels to the low-dose dexamethasone suppression test[2].

Leydig cell tumors of the ovary have a distinct androgen secretion pattern in relation to other tumors: they mainly produce testosterone and 5-alpha-dihydrotestosterone, with normal or slightly elevated urinary 17-ketosteroids. In comparison, lipid cell tumors secrete more androstenedione than testosterone and produce very high urinary 17-ketosteroids[14]. A more direct way to establish the origin of androgenic hypersecretion would be to catheterize ovarian and suprarenal veins simultaneously. However, this is a scarcely available invasive procedure, with a morbidity close to 5%, mainly associated to rupture or thrombosis of catheterized veins.

The feasibility of detecting virilising ovarian tumors by images depends on the type of tumor; they are generally similar to the neighboring structures[9]. Leydig cell tumors of the ovary are usually unilateral and small, resembling normal tissue[11,12]. They are often confined to the ovary, predominantly solid, not calcified, and not associated with ascites. Transvaginal and color Doppler ultrasound, as well as MRI, can detect tumors in a more effective way than conventional methods[1]. In the MRI, these tumors exhibit a low signal intensity on T1-weighted images, while the intensity on T2-weighted images varies according to the interstitial tissue content in stroma[15].

A definitive diagnosis can be established if histopathologic study reveals Reinke crystals, a pathognomonic feature of the Leydig cell tumor; however, it is only identified in 50% of cases[6,11]. Among the numerous immunohistochemical markers for ovarian tumors, inhibin and calretinin are the most useful, since many Leydig cell tumors express these markers. The epithelial membrane antigen is particularly useful to distinguish between clear cell carcinoma of ovary and kidney because antigen expression is higher in carcinomas compared to most steroid cell tumors[11].

Although Leydig cell tumors of the ovary are generally benign, they are at potential risk for malignant transformation. About 20% of patients develop metastasis, often limited to peritoneal cavity, and rarely in distant sites[11,12]. In cases of virilization due to elevated testosterone levels, oophorectomy must be considered after excluding adrenal causes[3]. Surgical intervention and removal allow confirming the diagnosis of Leydig cell tumor of the ovary and is followed by normalized testosterone levels and milder hyperandrogenism symptoms. Virilising effects disappear slowly, although clitoromegaly and voice changes may persist[5,12].

In conclusion, pure Leydig cell tumor is a rare malignancy, difficult to diagnose, that should be considered in women of reproductive age with elevated serum androgen levels and virilization. Its diagnosis is based on clinical features, elevated serum testosterone levels and imaging evidence of an ovarian tumor, and it is treated by oophorectomy.

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