Leydig Cell Tumor of Ovary in a Pre-Menopausal Woman: A rare case of Virilization.

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Cite this as:
BMCJ, 2015; 1(1): 24-26

Abstract

Background: Leydig cell tumor, a rare type of ovarian steroid cell tumor shows signs of virilization due to overproduction of testosterone. The condition is difficult to identify without histopathological examination. **Methods:** The authors report a case of Leydig cell tumor in a 34-year-old woman who first presented with severe clinical hyperandrogenism and associated complex medical history. **Results:** Investigations revealed markedly raised serum concentrations of total testosterone (680 ng/dL) (Normal reference values 02-45 ng/dL for adult woman), whereas prolactin, luteinizing hormone (LH) and follicle stimulating hormone (FSH), cortisol were all within the normal range. Transabdominal ultrasound and computed tomography (CT) scan of the pelvis and abdomen showed a bulky right ovary, but no other abnormalities. An ovarian source of androgens was suspected and surgery was arranged. The patient underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy. Histopathologically the case was diagnosed as Leydig cell tumor within the right ovary. After surgery, androgen levels returned to normal, and there was regression of the signs of virilization. **Conclusion:** Virilizing Leydig cell tumors usually have a benign behavior, with an excellent prognosis and reversion of symptoms after surgical treatment.

Keywords: Leydig cell tumor, virilization.

INTRODUCTION

Leydig cell tumors account for 0.1% of all ovarian tumors, and are a type of steroid cell tumor1. These tumors are uncommon but distinctive ovarian tumors of sex cord or stromal origin that often produce steroid hormones. Though polycystic ovary syndrome (PCOS) and nonmalignant androgen excess disorders are common causes of hyperandrogenism, other aetiologies such as ovarian or adrenal tumors have to be excluded. Leydig cell tumors and hilus cell tumors are distinctive functioning ovarian tumors that produce testosterone leading to hyperandrogenism and virilization in women.[1]

These typically occur in post menopausal women. The average age is 58 years and almost all patients are over 30 years of age. The usual presentation is with hirsutism or signs of virilization such as acne, hair loss, deepening of voice, a male body contour or hypertrophy of the clitoris. The serum testosterone concentration is elevated in virilized patients, but urinary 17-ketosteroids are generally within normal limits.[2] Non virilized patients have amenorrhoea or posmenopausal bleeding, depending on their age. Some Leydig cell tumors are found incidentally during surgery for some other condition. The endometrium may show hyperplasia or even adenocarcinoma, most likely secondary to peripheral conversion of testosterone to estrogen. Symptoms are often present for several years before the diagnosis is made. This is because Leydig cell tumors are usually small and difficult to localize.[2] The diagnosis can be very difficult because the size of such tumors is often too small to be detected by imaging techniques.[3] The diagnostic role and impact on management of ovarian and adrenal venous sampling in women presenting with symptoms and signs of hyperandrogenism has recently been debated.[4]

The authors hereby report an uncommon case of ovarian Leydig cell tumor in a pre-menopausal woman with severe hyperandrogenism and virilization with an attempt to delineate the clinical features and characteristics of this tumor with respect to histological findings.

CASE REPORT

A young woman aged 34 years reported to Rajshahi Medical College Hospital in Gynecology OPD on 20/04/2014 with worsening history of hyperandrogenism and virilization for last 6 months. She was then admitted to Gyne & obstetric department in ward -23, Rajshahi Medical College Hospital, for proper diagnosis and appropriate treatment. She presented with severe facial and body

hirsutism, male-pattern baldness, receding hairline, and 4 years history of amenorrhoea. She was 2nd para, her last delivery was 6 years back. She had an intra-uterine device in situ as method of contraception. She reported rapid onset of virilization with hirsutism, androgenetic alopecia and deep voice starting one year back. Her medical history was complicated by ischaemic heart disease, hypertension, hypercholesterolaemia, osteoarthritis and anxiety disorder with prominent agoraphobia. She admitted to be a non-smoker and consumed no alcohol.

Physical examination revealed signs of virilization with hirsutism androgenetic alopecia, and deep voice. Her weight was 70 kg and height was 161cm and blood pressure was 130/90mmHg while on medications. Gynecological examination revealed an enlargement of the clitoris and no palpable adnexal masses. She had no features of Cushing syndrome. Initial biochemistry included baseline hormone profile, amenorrhoea work-up including prolactin, estradiol, luteinizing hormone (LH) and follicle stimulating hormone (FSH), total serum testosterone, cortisol, thyroid function tests and liver function tests. Endocrine evaluation revealed hyperandrogenism, with markedly increased total serum testosterone (680 ng/dL) (Normal reference values 02-45 ng/dL for adult woman[1]). Serum levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH) were inappropriately low for a pre-menopausal woman with high levels of estradiol.

Liver function test showed raised cholesterol (9.6mmol/l) and triglyceride (6.1mmol/l), and normal HDL (0.87 mmol/1). Transabdominal ultrasound scan of the pelvis and abdomen showed normal findings, although the right ovary (6.5 x 5.8 x 5.8 cm) was reported was reported as being larger compared with the left ovary (3.2 x 2.9 x 2.8 cm). These findings were confirmed by computed tomography (CT) scan. An ovarian source of clinical and biochemical hyperandrogenism was suspected. The patient was therefore advised to undergo surgery in the form of total abdominal hysterectomy & bilateral salpingo-oophorectomy, and all the specimens were sent to department of pathology, Rajshahi Medical College Hospital for histopathological diagnosis.

(Figure 1). Other parts of the specimen showed no gross abnormality. Histopathological examination in right ovary revealed tumor cells arranged in lobules separated by fibrous septa (Figure-2). The tumor cells were round to polygonal with abundant eosinophilic cytoplasm and round nuclei with prominent nucleoli (Figure-3). These findings confirmed the diagnosis of Leydig cell tumor.

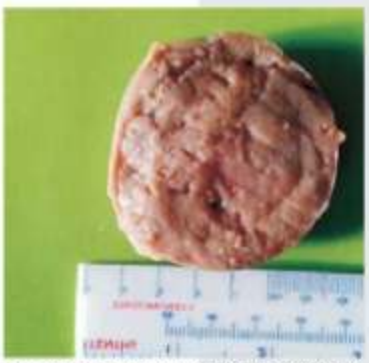

Figure1: A well circumscribed nodular mass with grey yellow glistening surface.

The pre- operative elevated androgen levels normalized following surgery. Post-operatively, the clinical signs of hyperandrogenism improved significantly. At 6-month follow-up, the patient remains fit and well, with significantly improved signs of virilization and completely resolved anxiety.

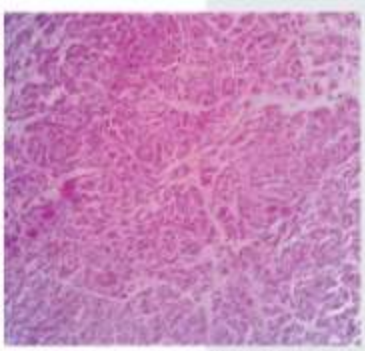

Figure 2 Photomicrograph showing tumor cells arranged in lobules separated by fibrous septa (Haematoxylin and eosin, × 40)

DISCUSSION

Most androgen secreting ovarian tumors are sex cord stromal tumors, which constitute less than 5% of all ovarian neoplasms.5 According to the World Health Organization (WHO) histologic classification of ovarian tumors, sex cord stromal tumors can be classified as granulosa stromal cell tumors, Sertoli stromal cell tumors, mixed sex cord stromal tumors and steroid cell tumors.6 Steroid cell tumors were also designated as "lipid cell tumors" but this term is not recommended because upto 25% of tumors in this category contain little or no lipid. The term "steroid cell tumor" has been accepted by the WHO because it reflects both the morphological features of the neoplastic cells and their propensity to secrete steroid hormones. Leydig cell tumors are rare ovarian steroid cell neoplasms composed entirely or predominantly of Leydig cells.6

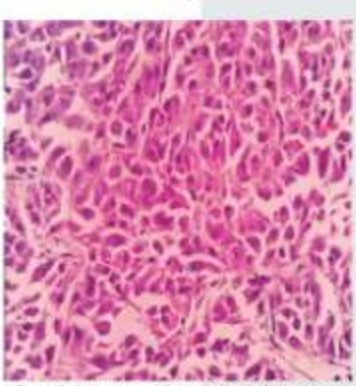

Figure 3 Photomicrograph showing round to polygonal tumor cells with abundant eosinophilic cytoplasm and round nuclei (Haematoxylin and eosin, × 400)

In the hilar zone, the Leydig cells can be normally found in 80% to 85% of the postpubertal ovaries, usually in association with non-myelinated nerve fibres. Hilar Leydig cell tumours arise from these preexisting Leydig cells of the hilus and can extend into the ovarian stroma depending on the size of the tumor. These tumors are generally benign and are usually unilateral.7 The stromal-Leydig cell tumors take their origin in the cortex or subcortical region in the ovary from ovarian stromal cells, which have differentiated into Leydig cells. They are very rare benign tumors. Like hilus tumors they also occur in postmenopausal patients and are unilateral.7

Though Leydig cell tumors typically occur in post menopausal women in this case the woman was aged 34 years of young lady- a rare case scenario. However unilateral location for this tumor is supported by our case report. These tumors secrete testosterone and occasionally oestrogenic activity may be observed. The androgenic manifestations are milder than those associated with Sertoli-Leydig cell androblastomas and their onset is less abrupt. Oestrogenic manifestations, such as irregular menses or postmenopausal bleeding have also been reported.8

The differential diagnosis of the Leydig cell tumors includes ovarian neoplasms containing Leydig cells or luteinized stromal cells. Sertoli-Leydig cell androblastoma occasionally exhibits predominance of Leydig cell component. But presence of Sertoli cells excludes the diagnosis of pure Leydig cell neoplasm. Stromal luteoma is a distinct type of steroid tumors arising in the ovarian stroma which resembles Leydig cell neoplasms.

Androgen producing tumors should be suspected in women with virilizing clinical symptoms and high testosterone levels. Sertoli Leydig cell tumors are larger and usually found easily on imaging, whereas hilar Leydig cell tumours are smaller and often difficult to find on imaging. If clinical suspicion is high exploratory laparotomy is indicated. It is noteworthy that in this era where sophisticated and expensive histopathological methods including immunohistochemistry are available, this rare and benign tumor can be diagnosed with high accuracy on good quality haematoxylin and eosin stained slides.

Conclusion

This case-report confirms that androgen-secreting ovarian tumors have to be considered amongst other disorders causing virilization in peri-menopausal and reproductive age women. Appropriate diagnostic approach encompassing clinical presentation, conventional biochemical, imaging methods & finally histopathological dignosis is paramount.

Acknowledgements

The authors would like to acknowledge the patient and all those who had been actively involved in the managements of this patient.

Competing interests

The authors declare that they have no competing interests.

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