

Postmenopausal hyperandrogenism of ovarian origin: A clinicopathologic study of five cases

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ABSTRACT

In postmenopausal women presenting with virilization and elevated testosterone levels, laparoscopic salpingo-oophorectomy should be considered after exclusion of adrenal causes. A clinicopathological study was conducted among those women who presented with features of hyperandrogenism in our postmenopausal clinic over a period of 2 years. Relevant past medical and surgical histories were elicited. Basic hormonal evaluation and radiological imaging were done. Laparoscopic bilateral salpingo-oophorectomy was done. Six weeks postoperatively, serum testosterone was undetectable with significant clinical improvement. There was no recurrence of symptoms during the follow-up period of 2 years. Treatment of postmenopausal women with hyperandrogenism and virilization with laparoscopic bilateral salpingo-oophorectomy is effective if she has no pronounced ovarian enlargement or adrenal tumor on imaging. An extensive endocrine testing and a detailed search for metastatic disease may be unnecessary.

Key Words: Hyperandrogenism, laparoscopic, oophorectomy, ovarian, postmenopausal

INTRODUCTION

A hyperandrogenic phenotype has a detrimental effect on quality of life in postmenopausal patients as increased facial hair and loss of scalp hair may cause emotional and psychological distress. It is often related to ovarian stromal disorders. Androgen-secreting tumors account for <1% of all ovarian tumors and most of them are benign making bilateral salpingo-oophorectomy the procedure of choice. We present a clinicopathological study of five cases of postmenopausal hyperandrogenism reported in a tertiary care center in North Kerala, over a period of 2 years (2010–2012).

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Access this article online

Quick Response Code:



Website:
www.jmidlifehealth.org

DOI:
10.4103/0976-7800.195699

CASE REPORT

There were two cases of stromal luteoma, one case of Leydig cell tumor, one case of ovarian hyperthecosis, and one case of Sertoli-Leydig cell tumor (SLCT). All of them had rapid improvement of symptoms and normalization of androgen levels following surgery. None had recurrence during the follow-up period of 2 years.

A 70-year-old nulliparous woman presented with gradual onset of hyperandrogenism (Ferriman–Gallwey [FG] score 20) for 10 years [Figures 1 and 2]. Hormonal evaluation showed elevated testosterone (8 nmol/L) and normal dehydroepiandrosterone sulfate (DHEAS) (150 mcg/dL). Imaging studies showed normal adrenals and no clinical

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How to cite this article: Ajith S, Beena G, Mathew NM, Omana EK. Postmenopausal hyperandrogenism of ovarian origin: A clinicopathologic study of five cases. J Mid-life Health 2016;7:189-92.

features of Cushing syndrome noted. Laparoscopic bilateral salpingo-oophorectomy was done. Intraoperatively, both ovaries were grossly looking normal. Histopathology showed polygonal cells with eosinophilic to foamy cytoplasm and dark-stained nuclei with mild pleomorphism suggesting steroid cell tumor – stromal luteoma type [Figures 3 and 4]. There was marked improvement in symptoms and hormone levels following surgery.

A 63-year-old P3L3 woman presented with gradual onset of hyperandrogenism (FG score 18) for 5 years. Hormonal evaluation showed elevated testosterone (7.5 nmol/L) and normal DHEAS (123 mcg/dL). After ruling out adrenal cause for the pathology, laparoscopic bilateral salpingo-oophorectomy was done. Intraoperatively, left ovary was larger, whitish, and irregular. Cut section – grayish with brownish area 0.5 cm in diameter. Smaller right ovary had similar appearance. Histopathology suggested stromal luteoma.

A 68-year-old P3L2 woman presented with gradual onset virilization (FG score 14) for 3 years. Hormonal evaluation showed elevated testosterone (8.4 nmol/L) and normal DHEAS (84 mcg/dL). There were no features of Cushing syndrome and adrenal imaging was normal. Laparoscopic bilateral salpingo-oophorectomy was done. Intraoperatively, right ovary was comparatively larger. Histopathology showed cells with abundant granular eosinophilic cytoplasm, well-defined nuclear membrane, and patent nucleoli. Some cells showed pigmented lipochrome in their cytoplasm. There was no evidence of vascular invasion. Reinke crystals were identified suggesting Leydig cell tumor-hilar type.

A 65-year-old P2L2 woman presented with postmenopausal bleeding. She had hirsutism of gradual onset for 5 years. Hormonal evaluation showed elevated testosterone (9 nmol/L) and normal DHEAS (115 mcg/dL). There were no features of Cushing syndrome and adrenal imaging was normal. Hormonal evaluation showed



Figure 1: Clinical manifestations of hyperandrogenism - hirsutism

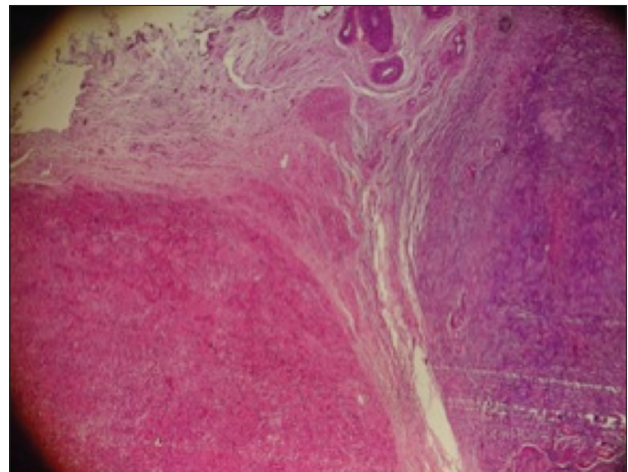


Figure 2: Low power microscopic view of stromal luteoma of ovary separated from normal ovarian tissue by fibrous septa

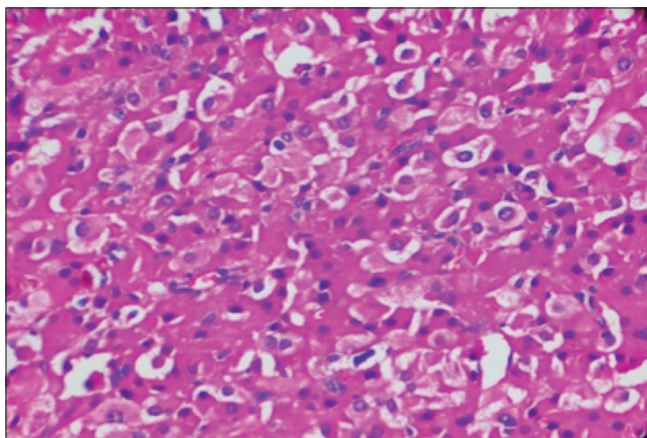


Figure 3: High power microscopic view of stromal luteoma of ovary showing round to polygonal cells arranged in nests with central round nucleus and moderate to abundant clear to eosinophilic cytoplasm

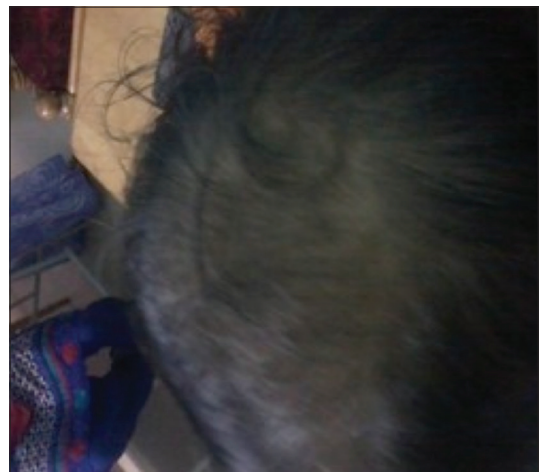


Figure 4: Clinical manifestations of hyperandrogenism - alopecia

elevated estradiol in addition. Endometrial evaluation showed proliferative endometrium. Laparoscopic bilateral salpingo-oophorectomy was done. Intraoperatively, both ovaries were enlarged and pearly white in color. Histopathology was suggestive of bilateral ovarian hyperthecosis. She was asymptomatic for a follow-up period of 2 years.

A 67-year-old P3L3 woman presented with rapidly progressing hirsutism for 2 years. Hormonal assay showed elevated DHEAS levels (635 mcg/dL) and normal testosterone levels (4 nmol/L). Magnetic resonance imaging showed a left adrenal mass for which left adrenalectomy was done which was unremarkable. There was persistence of hirsutism even after surgery. After 6 months, whole-body positron emission tomography-computed tomography revealed a suspicious enhancing lesion in the right ovary. Hysterectomy with bilateral salpingo-oophorectomy was done. Intraoperatively, the right ovary was of normal size with a central brown area of 7 mm. Histopathology suggested SLCT.

DISCUSSION

The management of hyperandrogenism in postmenopausal women is often quite challenging, especially for the source whether it is the ovary or the adrenal gland. Testosterone levels were elevated in all cases (reference values <2.6 nmol/L) and adrenal cause is ruled out by DHEAS levels (normal levels 15–150 mcg/L) and imaging studies. Surgical removal offers a confirmatory diagnosis and cure in such women.

Steroid cell tumors account for <0.1% of all ovarian tumors. They include (1) stromal luteoma, (2) steroid cell tumor, not otherwise specified (NOS), and (3) Leydig cell tumors.^[1] Stromal luteomas constitute 20% of steroid cell tumors. It is usually benign. They originate from luteinized cells or their precursors or undifferentiated spindle cells of the ovarian stroma.^[2] About 60% of cases present with estrogenic manifestations and only 12% cases are androgenic.^[3] Some cases have been reported with estrogenic manifestations such as endometrial hyperplasia and well-differentiated endometrioid adenocarcinoma.^[3] Stromal hyperthecosis has been found in association with stromal luteoma in the contralateral ovary in 90% of cases.^[4] Leydig cell tumors are rare ovarian steroid cell neoplasms which include hilar and nonhilar type.^[5] They present with progressive virilization by hyperproduction of testosterone. These are mostly benign and can be managed by oophorectomy. Steroid cell tumors, NOS are rare ovarian sex cord stromal tumors which are mostly benign but with malignant potential in premenopausal women.

SLCT or arrhenoblastoma is a rare ovarian tumor (0.1%–0.5%) in women of reproductive age and one-third are associated with androgen secretion. Some cases can benefit from adjuvant therapy with gonadotropin-releasing hormone analogs.^[6] Recent studies have shown that many cases of SLCT of the ovary are caused by germline mutations in the DICER1 gene. These hereditary cases tend to belong to younger age group.

Ovarian hyperthecosis is a rare nonmalignant cause of postmenopausal hyperandrogenism. The differentiation of ovarian interstitial cells into steroidogenically active luteinized stromal cells lead to elevated serum testosterone levels.^[7] There is associated hyperestrogenism. The hallmark of this syndrome is an increase in bilateral ovarian volume.^[8] There will be associated hyperinsulinemia and insulin resistance in almost all cases. They are at risk of metabolic complications of hyperlipidemia and type 2 diabetes.

CONCLUSION

Our cases illustrate that most cases of virilizing ovarian tumors in a postmenopausal woman are benign making bilateral salpingo-oophorectomy an appropriate cure. They can be small and elude imaging studies. Laparoscopic bilateral salpingo-oophorectomy may be regarded as the procedure of choice in a postmenopausal women with symptomatic hyperandrogenism, virilization, or both, who has no obvious ovarian or adrenal mass.^[9,10] This approach avoids unnecessary investigations and delays in definitive management. Since preoperative probability of malignancy is extremely remote, extensive imaging procedures for metastatic disease, and open laparotomy are unnecessary. Moreover, the availability of both ovaries for pathological examination allows detection of a rare malignancy and guides further therapy.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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