A Rare Case of Virilizing Ovarian Steroid Cell Tumor in a 46 year-old Woman: A Case Report and Review of Literature

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ABSTRACT

Virilization is the masculinization and enhancement of male secondary sexual characteristics in females. The etiology may be of adrenal or ovarian in origin. This case report shows a 46 year old woman who presented with defeminizing and virilizing symptoms. Further laboratory investigations revealed increased serum androgen levels and normal CT scan of the adrenals and kidneys. An ovarian mass was confirmed by transrectal ultrasonography. Following a total abdominal hysterectomy and bilateral salpingooophorectomy, histopathological and immunohistochemistry studies on the left ovarian mass confirmed an androgen-secreting, *steroid-cell tumor, not otherwise specified (NOS)*. Serum testosterone values abruptly declined to normal levels within 1 month post-surgery. This paper likewise discusses an extensive review of literature regarding this rare ovarian tumor.

Keywords: steroid cell tumor not otherwise specified, virilization, immunostaining

INTRODUCTION

Ovarian steroid cell tumors not otherwise specified (NOS) are very rare functioning sex cord stromal tumors of the ovary, comprising less than 0.1% of all ovarian tumors.[1] These tumors should be considered a cause of precocious puberty in children, and virilization in adults. In literature, only a few case studies of ovarian steroid cell tumors, NOS are reported, and this is only the third known case in our institution. A search through Philippine publications using HERDIN NeON showed only 1 published case of steroid cell tumor in the country, thus far.

Herein, we present a case of a 46 year old female with ovarian steroid cell tumor, NOS, who presented with defeminization and virilization secondary to supraphysiologic serum androgen levels, and subsequently had a successful response to surgery on follow-up. This case report also discusses aspects of the clinical presentation, diagnosis, differential diagnosis, histopathology, immunohistochemistry stains, malignancy potential, and treatment for these kinds of tumors.

CASE REPORT

A 46 year-old Filipino nulligravid presents with defeminization and virilizing symptoms since one year prior to admission. She is a known hypertensive and diabetic. She has undergone left total lobectomy, isthmusectomy, left periparotidectomy and partial right lobectomy for Multiple Adenomatous Colloid Goiter in 2009. She has been on regular follow-up with her endocrinologist to monitor her thyroid function tests. She also has regular check-ups with her obstetrician-gynecologist for monitoring of a physiologic left ovarian cyst, and irregular menstrual cycles, for which her physician reassured her that she was just in the "perimenopausal stage".

One year prior to admission, patient began to manifest breast atrophy, loss of female curves, deepening of voice, hirsutism, and male pattern baldness. She initially consulted an endocrinologist due to the persistence of her symptoms, particularly the progressive thinning of her hair. Work-ups were done in line with an initial impression of an adrenal tumor. Testosterone and Dehydroepiandrosterone sulphate (DHEAS) levels were increased, while Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH) and Estradiol (E2) were within normal limits (Table 1). CT scan of the abdomen revealed normal adrenal glands with no abnormal masses noted. There was minimal ascites with right sided pleural effusion. Transrectal ultrasound showed a left ovarian mass which was predominantly solid, with areas of hypoechoicity measuring 6.91 x 5.23 x 8.22 cm (Figure 1). The right ovary measured 3.13 x 1.97 x 3.61 cm, with multiple small follicles lining the edges of the stroma. The uterus, cervix, and endometrium were all normal. Sonographic impression was Ovarian New Growth, probably malignant. She was then referred to an obstetrician-gynecologist. Serum tumor markers revealed an increased level of CA-125 and normal alpha fetoprotein levels (Table 2).

On examination, the patient was moderately built with a body mass index of 25 kg/m^2. She had a low-pitched female voice. Head and neck examination showed male pattern baldness and facial hair (Figure 2), with no

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Table 1. Preoperative serum hormone values

Hormone	Patient Values	Normal serum values
Testosterone	5.21 ng/ml	0.3-0.7 ng/ml
DHEAS	11.79 mmol/L	0.96-6.95 mmol/L
Estradiol	63.58 pg/ml	12.5-166 pg/ml
LH	2.62 mIU/ml	2.4-12.6 mIU/ml
FSH	5.53 mIU/ml	3.5-20 mIU/ml

Table 2. Preoperative serum tumor markers

Tumor Markers	Patient Values	Normal serum values
CA 125	426.02 IU/ml	0-35 IU/ml
Alpha fetoprotein	1.85 IU/ml	<40IU/ml

anterior neck mass palpated. The patient had hirsutism affecting the chest, forearms, thighs and anterior abdominal wall with a modified Ferriman Gallwey Score of 26. She had a blood pressure of 130/90 mmHg. Chest and abdominal examination revealed bilateral breast atrophy, with a soft, non-enlarged and non-tender abdomen. On pelvic examination, patient had enlarged clitoris (Figure 3), and a 6x5 cm movable mass at the left adnexa. The plan was to do total abdominal hysterectomy, bilateral salpingooophorectomy with frozen section and possible bilateral lymph node dissection, and paraaortic lymph node sampling.

Intraoperatively, there was 300cc clear, yellowish ascitic fluid. No lesions were noted in the liver, subdiaphragmatic surface, omentum, pelvic sidewalls and cecum. The left ovary was converted to a 5 x 5 cm solid, lobulated mass, with yellowish cut surface (Figure 4). Frozen section of the left ovary revealed a histopathologic diagnosis of fibrothecoma. The right ovary was densely adherent to the intestines. A frozen section of the right ovary was likewise requested to rule out malignancy and revealed endometriosis of the right ovary. The uterus, cervix and both fallopian tubes were grossly normal. Final histopathologic diagnosis is Steroid Cell Tumor, grade 1, Not Otherwise Specified (NOS). The patient's post-operative course was unremarkable and she was subsequently discharged improved on the 2nd post-operative day.

The patient's serum total testosterone decreased to within normal levels within 1 month post-surgery (Figure 5). Three months post-op, patient showed gradual regression of abnormal hair pattern, deep pitch voice, and male pattern baldness. The patient is being followed up regularly with measurement of hormone levels as marker of recurrence.

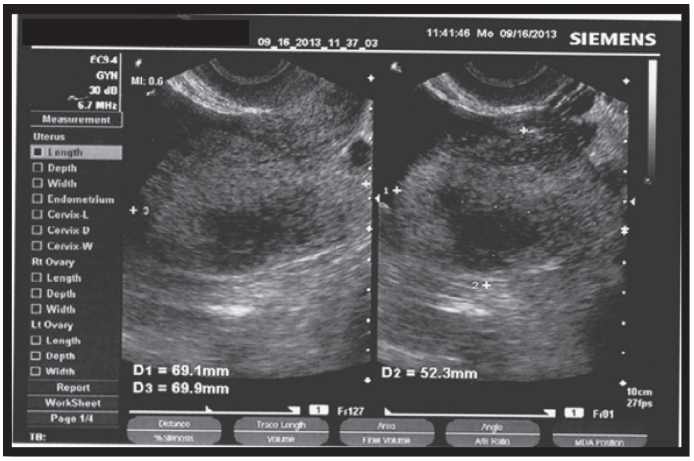

Figure 1. Transrectal ultrasound showing a left ovarian mass which was predominantly solid with areas of hypoechoicity, measuring 6.91 x 5.23 x 8.22 cm. This was signed out as Ovarian New Growth, left, probably malignant.

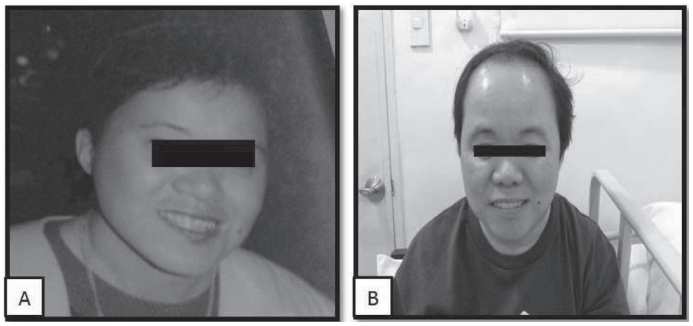

Figure 2. The patient's facial features before (A) and after (B) her virilizing symptoms manifested. Note the significant male-pattern baldness.

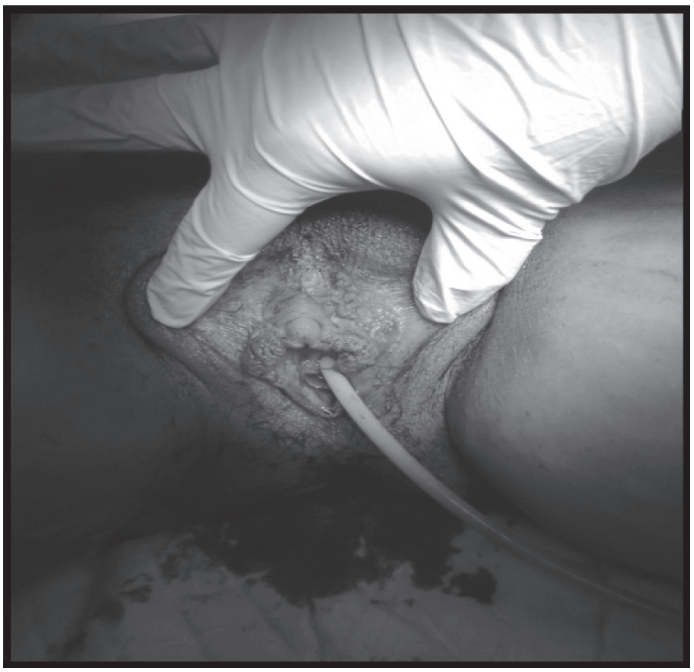

Figure 3. Patient manifested enlarged clitoris.

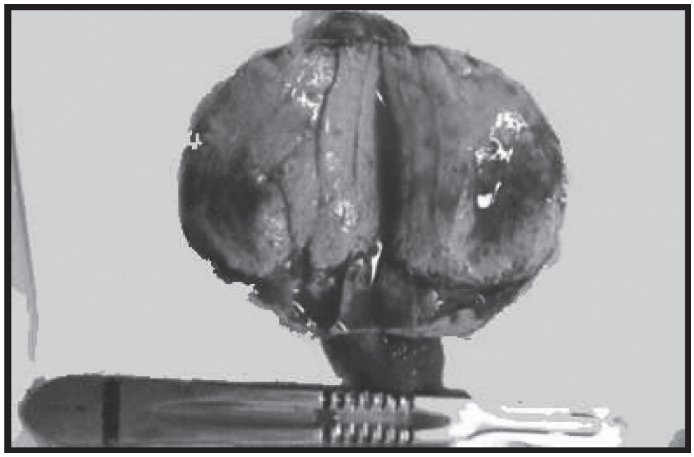

Figure 4. The left ovary was converted to a 5 x 5 cm solid, lobulated mass, with yellowish cut surface.

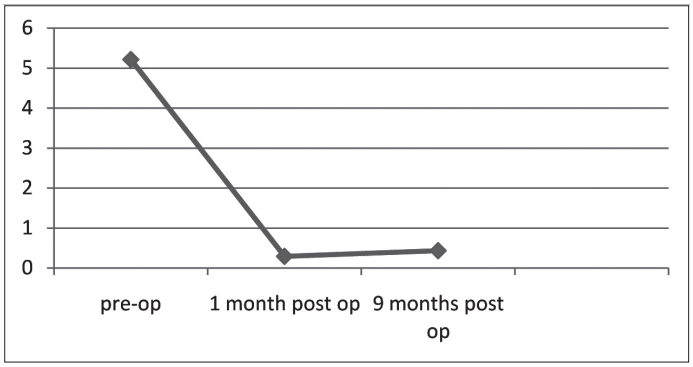

Figure 5. Serum Total Testosterone levels pre-op and 1 month post-op. *Note the abrupt reduction in testosterone levels.*

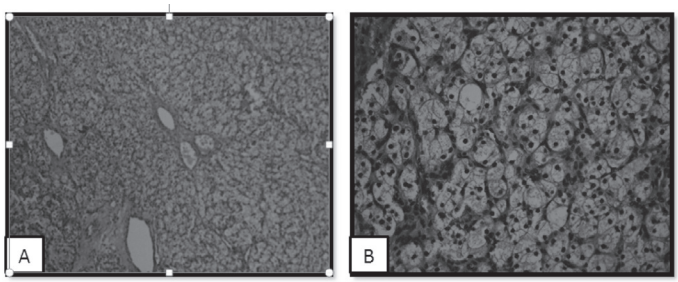

Figure 6. Photomicrographs of the left ovarian mass, at A) LPO (10x, H&E stain) and B) HPO (40x, H&E stain).

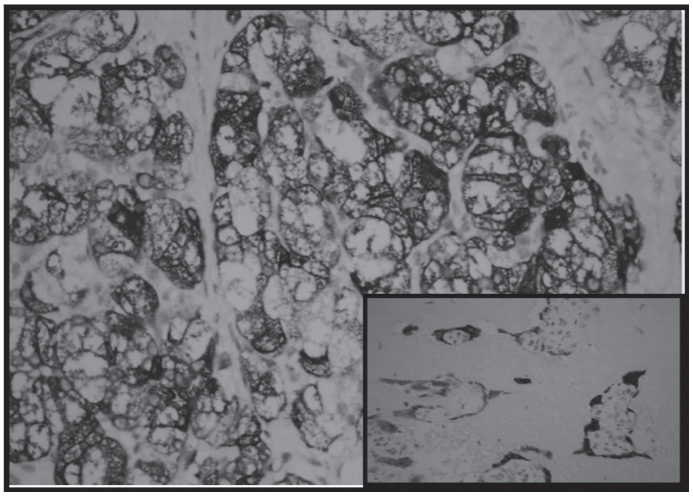

Figure 7. Photomicrograph of Inhibin immunostaining showing positive reaction. Inset: inhibin control (HPO, 40x)

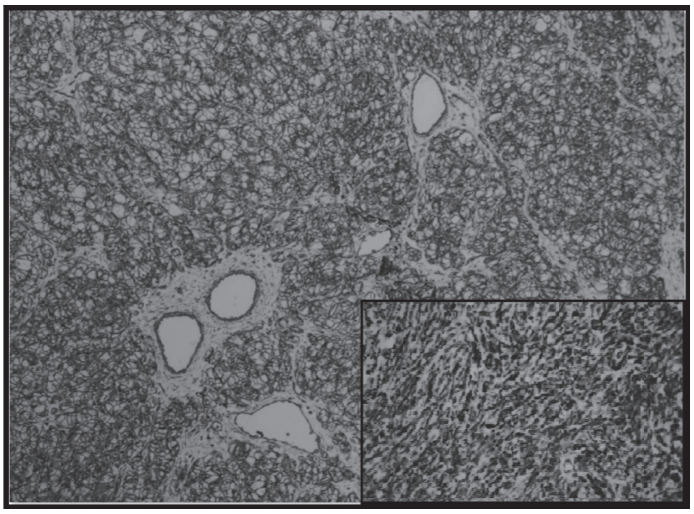

Figure 8. Photomicrograph of Vimentin immunostaining showing positive reaction. Inset: Vimentin control (LPO, 10x)

Ovarian Histology

Microscopic examination (Figure 6) showed large polygonal tumor cells arranged in diffuse sheets or in nests, separated by a rich vascular network. The tumor cells had small round nuclei, and abundant vacuolated cytoplasm, with no significant mitotic activity noted. Crystals of Reinke, which are usually seen in hilus cell tumors and leydig cell tumors, were not seen.

Immunohistochemistry staining (Figures 7 to 11) was positive for inhibin, anti-vimentin and cytokeratin, and negative for melan-A (ruling out renal cortical carcinoma or melanoma) and Epithelial Membrane Antigen (ruling out clear cell carcinoma and metastatic renal cell carcinoma), providing evidence in favour of a benign primary ovarian steroid cell tumor.

DISCUSSION

Virilization is the masculinization and enhancement of male secondary sexual characteristics in females.[1] A comprehensive work-up of a patient who manifests with virilization should include evaluation of an adrenal and ovarian source of pathology for the hyperandrogenism. Elevated serum androgen levels warrant abdominal and pelvic imaging with ultrasound, CT scan or MRI, to look for possible mass lesions that possibly supply the excess virilizing hormones.[2] In our patient, *Dehydroepiandrostiene sulfate and testosterone levels were both increased. A testosterone level of ≥ 2 ng/ml, as seen in our patient, is usually attributed to an androgen-secreting tumor and makes virilization caused by Polycystic Ovarian Syndrome*

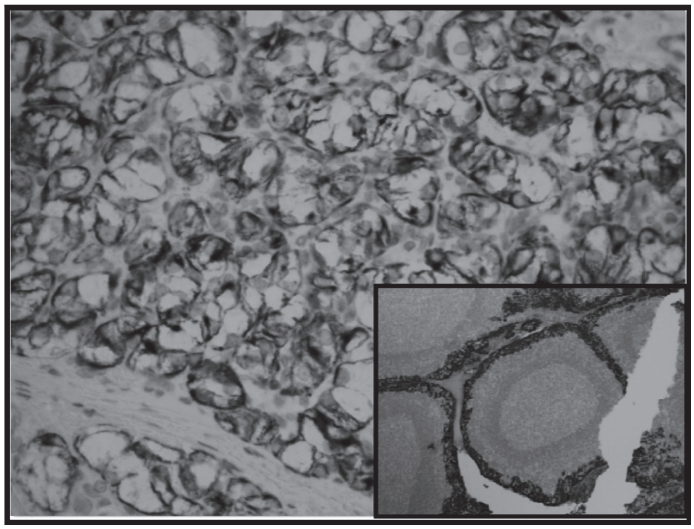

Figure 9. Photomicrograph of Cytokeratin (CK) immunostaining showing positive reaction. Inset: CK control (HPO, 40x)

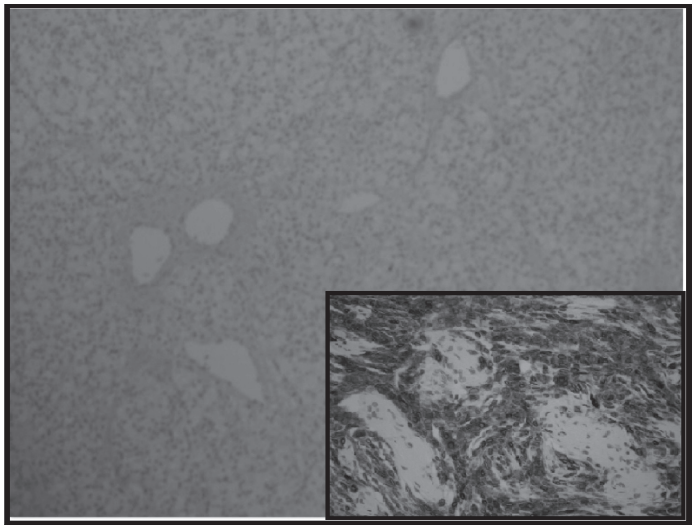

Figure 10. Photomicrograph of Melan-A immunostaining showing negative reaction. Inset: Melan-A control (LPO, 10x)

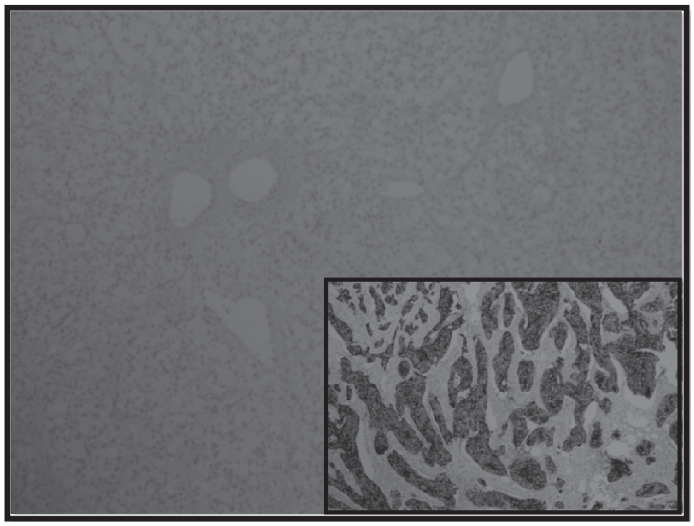

Figure 11. Photomicrograph of EMA immunostaining showing negative reaction. Inset: EMA control (LPO, 10x)

(PCOS) and stromal hypertrophy less likely.

A CT scan of the abdomen was then necessary to rule out an adrenal cause of virilization. The result showed no adrenal tumor, therefore excluding adrenal cause of virilization in our patient. An ovarian work up using a transrectal sonography finally showed an ovarian tumor, which then steered us to do surgical removal of the androgen-producing lesion. Final histopathologic diagnosis confirmed a virilizing tumor in the form of Steroid Cell Tumor, Not otherwise specified (NOS).

Epidemiology

Ovarian steroid cell tumors NOS are very rare sex cord stromal tumors of the ovary with malignant potential, accounting for less than 0.1% of all ovarian tumors. In literature only a few case studies of ovarian steroid cell tumors, NOS are reported, and this is only the third known case in our institution. A quick search of Philippine publications through PCHRD HERDIN NeON showed only 1 published case of steroid cell tumor who presented with hirsutism, virilization and polycythemia.[4]

Ovarian steroid cell tumors are usually benign, unilateral and characterized by a steroid cell proliferation, which account for the virilizing changes the patients manifest.[5] In the most recent World Health Organization (WHO) classification, these androgen-secreting steroid cell tumors are further classified as either (1) stromal luteoma arising from ovarian stroma, (2) leydig cell tumors (hilus cell tumor and leydig cell tumor non-hilar type) or (3) steroid cell tumors not otherwise specified (NOS), when the lineage of the tumor is unknown. [6,7]

Steroid cell tumors NOS usually occur in adults with an average age of 47 years old at the time of diagnosis. Non-specific clinical presentations may include abdominal pain or distention, bloating and ascites, but the more significant manifestations are those associated with its androgenic activity. Signs and symptoms of masculinizing tumors usually take place in two definite phases: An early phase of defeminization, and a subsequent phase of masculinization.[3] *In the case of our patient, she first noticed oligomenorrhea and amenorrhea, and breast atrophy* ***(defeminization phase)****, which then rapidly progressed to deepening of her voice, hirsutism, and male pattern baldness* ***(masculinization phase)****.*

Diagnosis

The diagnosis of steroid cell tumors NOS should be made on the basis of the clinical virilizing symptoms, the microscopic pictures, as well as immune reactivity to some immunohistochemical markers.[2] Immunohistochemistry helps in the distinction between steroid cell tumors of the ovary and other primary or metastatic ovarian neoplasms with oxyphilic, eosinophilic and clear cell histology[2], such

as in our case. *For our patient, immunostaining showed that the tumor cells stained positive for inhibin, cytokeratin and vimentin, which are the expected results for steroid cell tumors. The lack of stromal hyperthecosis and Reinke cells strengthened our diagnosis that this is indeed, steroid cell tumor NOS.*

Differential Diagnosis

Steroid cell tumors NOS must be distinguished from other tumors in the steroid cell category - stromal luteoma, and leydig cell tumors - and carcinomas, particularly primary clear cell carcinoma of the ovary, metastatic renal cell carcinoma, and even adrenal cortical carcinoma. [8,9]

Table 3 lays out the main differences between the three main types of steroid cell tumors. Essentially, the absence of Reinke cells and stromal hyperthecosis clinches our diagnosis of Steroid cell tumor NOS.

As for ruling out carcinomatas with similar eosinophilic clear-cell types, we rely on immunohistochemistry to rule these possibilities out. Immunostaining of the tumor cells stained negative on Epithelial Membrane Antigen (EMA) and Melan-A. Clear cell carcinoma and metastatic renal cell carcinoma are robustly positive to EMA and negative for inhibin, while adrenal cortical carcinoma generally have diffuse reactivity for Melan-A, effectively ruling these malignant differentials out.

Malignancy consideration

The most important factor to be determined in steroid cell tumors of the ovary is whether the tumor has malignant features or not.[3] Hayes and Scully reported on certain histopathological features which correlate highly with clinically malignant behavior. These being two or more mitotic figures per 10 high power fields, necrosis, a diameter ≥7 cms, hemorrhage, and grade 2-3 atypia.[10] *None of these were present in this case. Furthermore, the complete resolution of our patient's serum testosterone to normal levels following removal of the mass was also against the possibility of malignant ovarian deposits.*

Management

The mainstay of treatment of ovarian steroid cell tumor is surgery. In general, conservative surgery with unilateral oophorectomy and proper staging (if malignant) should be performed in women with stage 1 disease who desire future fertility, since these tumors are rarely bilateral. For women who have completed childbearing, total abdominal hysterectomy with bilateral salpingooophorectomy (with or without surgical staging) is indicated.[3,6] *Our patient is a 46 year old nulligravid, with no issues on future fertility, hence, TAHBSO was performed. Complete surgical staging nor post-op chemotherapy were not done, since both frozen and final specimens did not demonstrate any signs of malignancy*. Adjuvant chemotherapy should be based on the histologic appearance of the tumor and on its surgical stage. However, there are no well-defined chemotherapy guidelines for clinical management of malignant steroid cell tumor.[2]

Ideally, part of patient care for cases such as this, should include psychological support, either from a professional or the patient's family unit. Unfortunately, there seems to be a dearth of published literature regarding investigation on quality of life and psychological aspects of women with virilizing symptoms. It would be interesting to note what psychiatric disorders these patients may possibly suffer from due to their physical transformation, or how these patients cope with the stress of handling such conditions. Nevertheless, we, as primary care givers for patients stricken with this condition, should offer our patients emotional, and psychological support to help them deal with this life-changing event.

Table 3. Differential Diagnosis for Steroid Cell tumor, NOS.

Steroid cell tumor	Stromal Luteoma	Leydig cell tumor	Steroid cell tumor, NOS	Index case
Age	More common among post menopausal patients[7]	Average age: 58 years-old[7]	Average age: 47 years-old[3]	46 years-old
Symptoms	More commonly associated with estrogenic symptoms[7]	Virilization in 50% of cases[7]	Virilization in 50% of cases[7]	Virilization
Size	Rarely exceeds 3 cm[7]	Rarely exceeds 3 cm[7]	Larger in size, average size: 8.4 cm[7]	5 cm
Reinke crystals	(-)	(+)	(-)	(-)
Stromal hyperthecosis	(+)	(+)	(-)	(-)

CONCLUSION

Virilizing symptoms may be adrenal or ovarian in origin. These may be differentiated by doing initial laboratory tests measuring steroid hormones in the body, and imaging studies such as the CT Scan and ultrasound to confirm the presence of either an adrenal or ovarian mass. If it is ovarian in origin, then steroid cell tumors should be considered. Ovarian steroid cell tumors are usually benign, unilateral and characterized by a steroid cell proliferation, which account for the virilizing changes the patients manifest. Treatment usually involves surgery and symptoms regress post-surgery. However, it is also important to remember that benign as it may seem, the possible psychological impact of this illness to a patient needs to be considered, since these greatly affect physical appearances that affect one's morale and self esteem.

RECOMMENDATIONS

Since there is a lack of data in relation to steroid cell tumors in general because of its rarity, a registry/ census that takes note of its occurrence can be set into place. A support group may be formed such that patients undergoing this illness may find support in people who have had the same experience as they did.

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