CASE REPORT

An 88-year-old woman with flushing, alopecia and hirsutism and a Sertoli-Leydig cell tumour

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SUMMARY

Sertoli-Leydig cell tumour (SLCT) is a rare, androgen-secreting sex cord–stromal tumour of the ovary that usually occurs in young premenopausal women. The major clinical manifestations are virilisation and defeminisation. The following case describes an 88-year-old G1P1 woman, 40 years after menopause, who presented with flushing, hirsutism, voice changes and alopecia along with significantly elevated levels of testosterone. Postoperative report revealed a well-differentiated SLCT in the left ovary. This case is unique in that SLCT is a very rare cancer and even more so in an 88-year-old woman. Taking this case into consideration, it becomes reasonable to check androgen and oestrogen levels in postmenopausal women, not only in patients with signs of virilisation, but also in those with non-classical presentations, such as flushing or heat spells.

highlights the importance of considering an androgen-secreting tumour in the work-up of flushing in these patients.

CASE PRESENTATION

An 88-year-old G1P1 Caucasian female, former smoker, with a medical history of hypertension, chronic kidney disease, hypothyroidism and irritable bowel syndrome constipation type, presented to the endocrinology clinic with a chief complaint of flushing. Menopause occurred at the age of 47 without any vasomotor symptoms, such as heat flushes. Otherwise, her gynaecology history was notable for irregular menstrual periods and two episodes of abnormal uterine bleeding around the ages of 42 and 43 that required dilation and curettage. The patient's symptom of flushing, which she described as feeling hot in her entire body, especially the face, accompanied with increased redness of her skin but no pallor, was going on for 2 months before making her way to our office. These episodes occurred mostly after supper, continued throughout the night, and were associated with nausea and electrical shocks that climbed up her legs. She also noticed increasing blood pressure readings at home at the time, with systolic levels ranging in the 200s.

Additional symptoms included: vertigo (treated with physical therapy), diarrhoea, palpitations (unrelated to the hot flushes), brittle finger nails, frontal alopecia and hair growth on her face (chin and upper lip), arms and underarms as well as around her areola, lower abdomen and pubic area. She also noticed increasingly dry eyes and excessive weight loss—roughly 13 lbs in 2 months. Review of symptoms were positive for burning on urination, mood changes—increased agitation, anxiety and energy (she was able to knit 10 sweaters in a short period of time) and deepening of her singing voice. Pertinent negatives were that for headaches, rashes, abdominal pain and vaginal discharge/bleeding. She denied having similar episodes previously or family history of comparable complaints.

Physical examination at the time of her visit revealed a blood pressure of 164/88 mmHg on 60mg nifedipine and 0.1mg/24hours Catapres patch, coarse dark hair growth on her upper lip, anterior chin, bilateral forearms and lower abdomen, areas of decreased hair on the crown of her head and a receding hairline. Abdominal examination was unremarkable aside from well-healed surgical scars from a previous cholecystectomy and appendectomy. Pelvic examination was negative for an adnexal mass or clitoromegaly.

BACKGROUND

Neoplasms of the ovaries account for an overall 4% of all female cancers.¹ These tumours can be classified as either epithelial (malignant) or non-epithelial. The latter can be further subdivided into germ cell tumours, which includes teratomas and dysgerminomas among others, and sex cord–stromal tumours; Sertoli-Leydig cell tumour (SLCT) is one of the two sex cord–stromal tumours of the ovary.² It is a testosterone-secreting tumour that accounts for <0.5% of primary ovarian neoplasms.³ These tumours are generally unilateral in nature and elevated levels of testosterone and androstenedione can be seen in up to 80% of patients.^{3,4} The majority of these tumours, roughly 75%, occur between the ages of 20 and 30 years, with <10% occurring either prior to menarche or after menopause. While the incidence of these tumours is rare in women older than 65 years of age, some of the reported cases occurring in postmenopausal women presented with signs of virilisation, such as growth of facial hair, enlargement of the clitoris, deepening of the voice and pain in the lower part of the abdomen.⁵ The following case describes an 88-year-old postmenopausal woman who presented with a chief complaint of facial flushing and signs and symptoms of hyperandrogenism, corresponding to her high levels of serum testosterone. While she had a negative CT scan for an adnexal mass, she was later found to have an ovarian source through ovarian venous sampling, which was consistent with SLCT on pathology. This report presents a unique case of SLCT in a woman 40 years after menopause and

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Table 1 Serum and urine studies presurgery and postsurgery

	Parameter	First visit	1 month post surgery	Reference range
Serum levels	Testosterone (total)	1090 ng/dL 4 days later: 1307 ng/dL	6 ng/dL	2–45 ng/dL
	Testosterone (free)	198.4 pg/mL 4 days later: 295.4 pg/mL	0.6 pg/mL	0.2–3.7 pg/mL
	DHEA sulfate	58 µg/dL		7–177 µg/dL
	FSH	35.5 mIU/mL		25.8–134.8 mIU/mL (postmenopausal)
	LH	14.0 mIU/mL		14.2–52.3 mIU/mL (postmenopausal)
	Oestradiol	55.5 pg/mL		0–30 pg/mL (postmenopausal)
	Cortisol	20.2 µg/dL		AM: 5–23 µg/dL
Urine levels	5-HIAA	5.0 mg/24		≤6.0 mg/24
	Metanephrines	Metanephrine		Metanephrine
		24 hours: 203 µg/24 hours		24 hours: 224–832 µg/24 hours
		Normetanephrine: 138 µg/24 hours		122–676 µg/24 hours
	Catecholamines	Dopamine: 85 µg/24 hours		Dopamine: 52–480 µg/24 hours
		Norepinephrine: 12 µg/24 hours		Norepinephrine: 15–100 µg/24 hours
		Total epinephrine+norepinephrine: 12 µg/24 hours		Total epinephrine+norepinephrine: 26–121 µg/24 hours

5-HIAA, 5-hydroxyindoleacetic acid; DHEA, dehydroepiandrosterone; FSH, follicle-stimulating hormone; LH, luteinising hormone.

INVESTIGATIONS

Serum androgen and oestrogen levels, along with other laboratory tests (table 1), were notable for elevated levels of free testosterone at 295.4 pg/mL (reference range: 0.2–3.7 pg/mL), total testosterone at 1307 ng/dL (reference range: 2–45 ng/dL)—these were increased from the initial high values obtained 4 days prior, and serum oestradiol at 55.5 pg/mL (reference range: 0–30 pg/mL). Serum dehydroepiandrosterone sulfate (DHEA-S) was within normal limits (table 1). ECG showed sinus rhythm and an old myocardial infarction.

CT scan without contrast of the abdomen and pelvis showed no adnexal or colonic masses, and the ovaries, adrenals and kidneys appeared unremarkable. The uterus was lobulated, suggesting old fibroids, and the liver and spleen were notable for benign-appearing calcifications, suggesting possible granulomatous exposure. Transvaginal ultrasound was also negative for an adnexal mass or other pelvic organ abnormality. Because of the high testosterone levels, bilateral ovarian venous sampling was done, which confirmed high levels of testosterone coming from the left ovary, consistent with a testosterone-secreting ovarian tumour and/or hyperplasia.

TREATMENT

Eight months after the start of her symptoms, the patient underwent surgical treatment with robotic-assisted laparoscopic total hysterectomy and bilateral salpingo-oophorectomy. Pathology showed a final histological diagnosis of a well-differentiated SLCT in the left ovary. Immunohistochemical and morphological characteristics of the tumour are depicted in figures 1–3. The tumour specimen displayed numerous cells with nuclear

Figure 1 Immunohistochemical staining of the patient's Sertoli-Leydig cell tumour (SLCT). Low-power (×4) view of the SLCT found in the left ovary with residual ovarian tissue (black arrow).

pseudoinclusions (figure 2) and Reinke crystals (figure 3), features consistent with SLCT.⁶ The tumour was primarily composed of Leydig cells. The left ovary was slightly larger than the right, measuring at 2.8×1.8×1.5 cm versus that of 2.5×1.0×0.7 cm in the right. Other pathology results included: mild, chronic inflammation of the cervix, an endometrial polyp and fibroids in the myometrium. Endometrial lining was not significantly thickened at 4 mm in a background of proliferative and cystic changes, suggesting a response to increased oestrogen levels.

OUTCOME AND FOLLOW-UP

Free testosterone levels 3 weeks postoperatively decreased to 0.6 pg/mL while total testosterone declined to 6 ng/dL (table 1). The patient's status also improved postresection, with relief of many of her concerns: diarrhoea, excess hair growth, alopecia, nausea, skin redness and brittle nails. However, current complaints include a left-sided abdominal, burning pain that is worse at night without any other associated abdominal, vaginal or bowel symptoms. Physical examination postoperatively was also unremarkable aside from new, well-healed surgical scars.

DISCUSSION

Virilisation in a postmenopausal woman may be due to an increase in androgen production by either the ovary or the adrenal glands.^{6–8} However, differential diagnosis of hyperandrogenism in a postmenopausal woman includes Cushing's syndrome, medication-induced and non-classical adrenal hyperplasia. Imaging studies and serum levels of androgens (testosterone and DHEA-S) and other disease markers (eg, cortisol or 17-hydroxyprogesterone) can be useful in identifying the source of androgens in a woman presenting with virilisation.^{7,8}

Figure 2 A ×20 view of the tumour showing several cells with nuclear pseudoinclusions (black arrow) present in Leydig cell tumours.

Figure 3 High-power ($\times 40$) view of the patient's tumour, which demonstrates multiple cytoplasmic Reinke crystals within the tumour cells (black arrow) consistent with Sertoli-Leydig cell tumour.

The normal serum levels of DHEA-S and cortisol in our patient made an adrenal origin and Cushing's syndrome, respectively, less likely.^{6–8} However, the elevated levels of serum testosterone was more suggestive of an ovarian source, and one such type of androgen-producing ovarian tumour is SLCT, which on histopathological examination was revealed to be the source of androgens in our patient (figures 1–3).

SLCTs are a rare type of sex cord–stromal tumour of the ovary that predominantly occurs in young women and are uncommon after menopause.⁹ They account for roughly 1% of sex cord–stromal tumours and $<0.5\%$ of all ovarian neoplasms.⁸ These tumours are composed of a mixture of cells that morphologically resemble male Sertoli and Leydig cells and are found to be unilateral in 98% of patients.^{7,8} They mainly secrete testosterone, which can cause endocrine manifestations—seen in about half of the patients—of virilisation to appear.⁷ The clinical characteristics of SLCT have been found to be associated with the degree of histological differentiation,⁵ and these clinical signs and symptoms include that of defeminisation (amenorrhoea, oligomenorrhoea and breast atrophy) followed by that of progressive masculinisation (acne, deepening of the voice, hirsutism, temporal balding and clitoromegaly).^{5,9} Around 50% of SLCT cases come to clinical attention due to the latter manifestations of progressive masculinisation,⁴ as was seen in our patient. It has been reported that when the value of testosterone, mainly secreted by the Leydig cells of the tumour, exceeds 2 ng/mL, there is obvious evidence of virilisation.⁷ Our patient presented with initial total testosterone values as high as 1307 ng/mL, thus explaining many of her signs and symptoms of increased androgens.

While virilisation and defeminisation symptoms have been described in as high as 77% of cases,⁷ some reports have suggested signs and symptoms of hyperoestrogenism associated with SLCT, such as endometrial hyperplasia, abnormal uterine bleeding and menorrhagia/metrorrhagia.^{7,10} These symptoms were not seen in our patient, despite her slightly elevated oestradiol levels for a postmenopausal woman and proliferative endometrium on histology postresection. The latter findings are most probably explained by peripheral aromatisation of some of the excess testosterone.^{4,5} Since the patient is almost 40 years postmenopausal, she likely had a scant reservoir of ovarian follicular (granulosa) cells—the source for oestradiol production in a reproductive-aged woman.⁴ Although histological examination did not reveal endometrial hyperplasia, atypia or cancer from the unopposed endogenous oestradiol, which may be attributed to the early intervention in our case preventing any further exposure, it would have been helpful to obtain an oestradiol level

postoperatively; this would have confirmed androgen aromatisation as the source of excess oestradiol in our patient.⁴

Furthermore, androgen production, specifically testosterone, has been found to be associated with Leydig cell hyperplasia in the ovaries—seen in some postmenopausal females with normal pelvic imaging—and more rarely with mature cystic teratomas (dermoid cysts).⁸ Although our patient's CT scan of the abdomen and pelvis did not show a discrete mass in the ovaries, making Leydig cell hyperplasia a possibility, pathology results revealed SLCT. Nonetheless, the diagnosis of Leydig cell hyperplasia should be considered in postmenopausal women with hyperandrogenism and high levels of serum testosterone if imaging of the ovaries is found to be normal. Regardless, histopathological examination of the tumour is necessary for confirmation of the diagnosis.⁸

Since these tumours are rarely bilateral, found in $<5\%$ of cases and predominantly occur in young women of childbearing age—mean age is 25 years, conservative surgical removal of the tumour and adjacent fallopian tube is generally justifiable if preservation of fertility is desired and/or there is no evidence of extension beyond the involved ovary.⁵ Studies have found that SLCTs have malignant potential, and it is suggested that frozen section intraoperatively may help in deciding the appropriate management in patients undergoing such conservative surgical treatment.⁸ However, taking into account the age of our patient of 88 years and given her symptoms of hyperandrogenism, it was decided that she undergo total laparoscopic hysterectomy and bilateral salpingo-oophorectomy instead. This procedure was deemed sufficient, as pathology did not reveal malignant potential, such as poor differentiation, presence of heterologous elements, high mitotic counts or rupture of the tumour on pathology, and thus did not require further surgical staging.^{9,11} Furthermore, the choice to proceed with laparoscopy is suggested to be useful in SLCT management and detection of metastasis, as it allows for peritoneal cavity observation and sampling.⁷ Nonetheless, prognosis of SLCT is generally good and there is typically prompt return of feminine characteristics with excision of the tumour—while disappearance of masculinisation features is frequently slower.^{9,12} Our patient's hirsutism, excess arm hair growth, agitated mood, hair loss and nail changes improved 1 month postresection as her levels of testosterone declined to 6 ng/dL (table 1).

Interestingly, the patient's unique nail complaints of brittleness and change in appearance presurgery were found to be reported in another study by Moghazy *et al* and was termed the Al-Hendy nail sign. Per the authors, their patient's nails had appeared flattened with concave, spooned ends—similar to that seen in iron-deficiency anaemia. The authors subsequently conducted a study to evaluate for the presence of androgen receptors in healthy female nail-bed cells. They found that such receptors were located in samples of premenopausal women, suggesting that androgens might have a direct effect on human nail bed tissues.⁴ However, we did not carefully observe nor elicit the exact changes seen in our patient's fingernails, aside from her history of newly, easily breakable nails and vague description of a change in appearance, prior to surgery. Nonetheless, had we come on this study before the tumour resection, we would have been more thorough in examining and documenting her nail findings.

In addition to just performing surgery, the gold standard treatment of SLCTs,⁷ other treatment options include surgery with adjuvant chemotherapy and/or radiotherapy. This more aggressive therapy is indicated for advanced stage tumours and those with poor prognostic features mentioned above.⁹ Nonetheless,

it is important to follow-up with the patient for tumour recurrence, and thus, she is on a 6-month follow-up schedule with endocrinology.

Our patient's current symptoms of 'burning' of the insides as well as her whole body during the night may be explained by oestrogen withdrawal after the surgery, which can be consistent with the well-established cause of hot flushes.⁴ Once more, it would be helpful to obtain postoperative serum oestradiol levels to aid in the explanation of her postresection complaints. Nonetheless, the patient's initial presenting symptoms were hot flushes, particularly in the face; this may have another underlying mechanism or even a dynamic interaction between testosterone and its aromatisation into oestradiol. It would be interesting to further study a possible link between oestradiol and testosterone levels in leading to hot flushes and increased redness of the skin, as it may be another symptom associated with androgen-producing tumours.

In conclusion, SLCTs are overall rare ovarian tumours, and are even more so in postmenopausal women. Although mild hirsutism

and increased head hair loss may be a normal physiological response in a postmenopausal woman,⁶ a patient with signs and symptoms of virilisation should have serum androgen levels checked to work up for an androgen-producing tumour from either the ovaries or the adrenal glands. Moreover, a postmenopausal patient presenting with complaints of flushing and heat spells should also have serum androgens and oestrogens checked. Such elevated levels of androgens can, at times and as in this case, be the only preoperative clue to a diagnosis of an androgen-secreting tumour, even when a discrete mass or site of tumour cannot be found on imaging. In such a situation, ovarian and/or adrenal venous sampling may be useful in detecting the presence of a small tumour, thus allowing for early diagnosis and treatment.

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Learning points

- ▶ A postmenopausal patient with a complaint of flushing accompanied with signs/symptoms of virilisation may have an underlying androgen-secreting tumour and thus should be worked up with serum testosterone and dehydroepiandrosterone sulfate levels, along with supplementing laboratory tests to rule out other causes of either flushing and/or hyperandrogenism.
- ▶ Facial flushing and/or heat spells may be a non-classical presentation of elevated androgen levels, if no other virilising or defeminising symptoms are present and/or other causes of flushing have been rejected, and thus further work-up for an androgen source may be pertinent in such a patient's work-up.
- ▶ A patient with very high levels of serum androgens but a negative imaging study for a discrete adnexal or adrenal mass should have ovarian or adrenal vein sampling, respectively, to detect possible androgen-producing cell hyperplasia or small tumours.
- ▶ Conversion from an androgen to an oestrogen, a process known as aromatisation, is a well-established physiological mechanism, and it has been observed in various studies associated with Sertoli-Leydig cell tumours. Thus, in addition to obtaining serum androgen levels before and after surgery, detecting serum oestrogen levels before and after treatment can also be useful in determining the next best steps for a patient, specifically if she is a postmenopausal female, as exposure to excess oestrogen can put one at risk for breast cancer and/or endometrial hyperplasia/carcinoma among others.

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