Ovarian Leydig Cell Tumour Diagnosis in a Postmenopausal Woman with Uterine Bleeding: A Case Report and Literature Review

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Introduction

Leydig cell tumours are a rare subgroup of steroid cell tumours, accounting for approximately 0.1% of all ovarian tumours. These usually produce androgens and cause virilisation with signs of hirsutism, temporal balding, polycythaemia, and endometrial atrophy (Boehnisch *et al.*, 2019). Here, we present a case of a rare Leydig cell tumour with postmenopausal uterine bleeding due to oestrogenic effect and polycythaemia due to androgenic effect. Although the initial consultation was for postmenopausal uterine bleeding, additional screening revealed polycythaemia and virilisation leading to the diagnosis of an ovarian tumour. Additionally, we found improvement in polycythaemia after the surgical removal of the ovarian Leydig cell tumour.

Case

Ethical committee approval was unnecessary due to case report with anonymized personal information. A 57-year-old woman presented to our hospital with uterine bleeding 10 years post-menopause. Physical examination revealed obesity with a body mass index of 31 kg/m^2 and mild hypertension (154/94 mm Hg). Transvaginal ultrasonography showed endometrial thickening (10 mm); however, it was obscured by multiple uterine myomas with no visualisation of the ovaries. Although endometrial

cytology showed no abnormalities, several signs of virilisation were observed, such as hirsutism with a score of 13 by the Ferriman–Gallwey score and mild hair loss in the frontal region. Gynaecological examination revealed clitoral enlargement.

Magnetic resonance imaging (MRI) revealed a 30-mm solid mass, low to medium intensity on a T2-weighted image, and low intensity on a T1-weighted image, in the right ovary. Radiological findings suggested hormone-producing tumours, such as fibroma or thecoma. Laboratory tests revealed marked increase in haemoglobin (Hb, 19.9 g/dL, normal range 11.6–14.8 g/dL), serum oestrogen (57.0 pg/mL, normal range approximately 42 pg/mL), and testosterone (5.8 ng/dL, normal range 0.11–0.47 ng/dL) levels. Erythropoietin levels were normal (10.1 mIU/mL, normal range 4.2–23.7 mIU/ml), and genetic screening for the JAK mutation was negative.

Preoperative phlebotomy resulted in a decrease in her Hb levels from 19.9 g/dL to 18.5 g/dL. Total laparoscopic hysterectomy and bilateral adnexectomy were performed without any complications. Two months after surgery, the haemoglobin level dropped significantly to 15.7 g/dL, and the serum testosterone level decreased to normal (0.1 ng/dL).

Histopathology investigation revealed leiomyomas in the uterus, no malignant component in the endometrium, and no neoplastic changes in the left ovary. The right

ovary harboured large and small nodular structures separated by fibrous tissue. Immunostaining identified the mass as a benign, AR (+), calretinin (+), Melan-A (+), inhibin (+), CD99 (-) Leydig cell tumour with Reinke crystals.

Discussion

We encountered a case of Leydig cell tumour with a clinical presentation of postmenopausal uterine bleeding accompanied by polycythaemia and virilisation. Although several cases of bleeding have been reported in Sertoli–Leydig cell tumours, there is no report of a patient with Leydig cell tumour complaining of uterine bleeding (Table 1). As shown in Table 1, patients with Leydig cell tumours often have elevated serum oestrogen levels. The oestradiol level of Chen *et al.*'s (2018) patient was similar to ours and that of Kozan *et al.*'s (2014) case was much higher than in ours (Kozan *et al.*, 2014, Chen *et al.*, 2018). High serum testosterone level counteracts oestrogen effects on the endometrium. In our patient, the high testosterone levels were still lower than those reported in other cases. Therefore, uterine bleeding could have occurred owing to insufficient testosterone counteraction on the predominant oestrogen effect on the endometrium.

There are some reports of polycythaemia caused by Leydig cell tumours similar to this case (Nagamani and Gonzalez-Vitale, 1981, Yetkin *et al.*, 2011, Pelusi *et al.*, 2013, Kozan *et al.*, 2014). Erythropoietin-secreting uterine myomas have also been reported to cause polycythaemia (Suresh and Rizk, 2020). In this case, the serum erythropoietin level was normal. Polycythaemia vera was ruled out by genetic testing for mutations in the JAK locus. We believed that hyperandrogenism due to the Leydig cell tumour was the cause of her polycythaemia because erythropoietin production was absent, and her polycythaemia normalised after surgery.

Leydig cell tumours are usually unilateral and small in 95% of cases. As shown in Table 1, six of seven patients had tumour sizes with an average diameter of 4 cm. Small tumours are difficult to detect via ultrasonography and computed tomography, although symptoms may generally develop early, especially in cases of hormone-producing tumours (Monteagudo *et al.*, 1997). Hence, we strongly recommend MRI in cases wherein a hormone-producing tumour is suspected but cannot be confirmed by transvaginal ultrasonography.

Even if the result of endometrial cytology is not abnormal for postmenopausal uterine bleeding, further testing should not be neglected because a hormone-producing tumour should be suspected. Furthermore, it is important to check for other symptoms, such as

virilisation, and link them to the laboratory data. Although it is inherent for a physician, detailed interviews and careful medical examinations are critical for accurate diagnosis.

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Table 1 Previous reports of ovarian Leydig cell tumor

Case	Source	Age	Symptoms	Menopausal bleeding	Chief complaint	Tumor size	Laboratory data Pre-surgery→Post-surgery	Examination
1	Ozgil et al. (2010)	60	hirsutism polycythaemia baldness	no information	hirsutism male pattern baldness	14×11×9 cm	Testosterone >1600 ng/mL→44.4 ng/mL Estradiol (N.E.) EPO (-) Hb 18.9 g/dL→12.8 g/dL	Ultrasonography CT
2	Kozan et al. (2014)	55	polycythaemia thromboembolism virilisation baldness SAS	-	male pattern baldness hirsutism mild acne	37×41×35 mm	Testosterone >1600 ng/mL→0.2 ng/mL Estradiol 169 pg/mL→＜12 pg/mL EPO (20.3 mIU/mL) ↑ Ht 51%→42%	Ultrasonography CT
3	Chen et al. (2018)	60	hirsutism virilisation DM	-	hirsutism	15×16 mm	Testosterone 3.399 ng/mL→0.571 ng/mL Estradiol 51 pg/mL	Ultrasonography CT MRI
4	Pelusi et al. (2013)	68	hirsutism polycythaemia alopecia	-		normal	Testosterone >7.20 ng/mL Estradiol ↑	Ultrasonography CT PET-FDG
5	Pelusi et al. (2013)	58	hirsutism alopecia clitromegaly	-		4-5 mm	Testosterone >2.88 ng/mL Estradiol ↑	Ultrasonography CT
6	Pelusi et al. (2013)	60	hirsutism polycythaemia alopecia clitromegaly	-		35 mm	Testosterone >2.02 ng/mL Estradiol ↑	Ultrasonography CT
7	Present case		polycythaemia virilisation hypertension	+		30 mm	Testosterone 5.8 ng/mL→0.1 ng/dL Estradiol 57 pg/mL Hb 19.9 g/dL→15.7 g/dL EPO 10.1 mIU/mL	Ultrasonography MRI

Table 1 Previous reports of ovarian Leydig cell tumor

SI unit conversion: Testosterone SI = 0.03467 × ng/mL, Estradiol SI = 3.671 × pg/mL, EPO SI = 1.0 × mIU/mL, Hb SI = 10 × g/dL

Normal range: Testosterone: 0.11–0.47 ng/dL, Estradiol: approximately 42 pg/mL, EPO: 4.2–23.7 mIU/mL, Hb: 11.6–14.8 g/dL

N.E.: not examined, CT: computed tomography, MRI: magnetic resonance image, SAS: Sleep Apnea Syndrome