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Letter to the Editor

Hyperandrogenism revealing an unexpected granulosa cell tumor

Dear Editor,

We herein report a rare case of an ovarian androgen-secreting granulosa cell tumor in a 73 years old woman. Relevant past history comprises pT3N1M0 HER2 positive breast cancer 10 years ago treated by surgery followed by radiotherapy and Trastuzumab-Letrozole adjuvant therapy. She was referred to our endocrinology unit for further investigations regarding a 2 years history of hirsutism. Clinical examination revealed major hirsutism (Ferriman-Gallway score 36) and signs of virilization including frontal balding and clitoridomegaly. There was no associated Cushing syndrome.

Laboratories examinations showed a major elevation of serum concentration of total testosterone at 13.87 nmol/L (normal range: 0.52–2.42 nmol/L) with other androgens within normal range (DHEA, Androstenedione, 17-hydroxyprogesterone). Estradiol was elevated to 169 pmol/L (normal range in menopausal woman < 73 pmol/L). Midnight serum cortisol, Free Urinary Cortisol and 1 mg-Dexamethasone tests ruled out a Cushing Syndrome.

Abdominal CT scan and MRI did not visualize any adrenal or ovarian abnormality in volume shape or contrast enhancement. Ovarian volume was within normal range. Endometrial wall was thickened (7 mm). Secondary bone lesions were suspected on both cervical and lumbar spine. Investigations were completed by a bone scintigraphy and a 18 FDG PET scan that confirmed hypermetabolic nature of the vertebral localizations, but did not show any ovarian or adrenal tumor. A biopsy asserted the diagnosis of bone metastasis of primary mammary carcinoma.

Regarding the management of hyperandrogenism, a laparoscopic bilateral oophorectomy was performed with patient's informed consent. Histopathological analysis showed clinically and macroscopically normal ovaries. Histopathological analysis revealed a 5 mm right intra ovarian sex cord-stromal tumor. The small patternless proliferation consisted of cells with characteristic coffee bean-shaped nuclei suggesting a granulosa cell tumor (Fig. 1). Inhibin and Calretinin positivity supported this hypothesis.

Post-operative testosterone and estradiol level lowered down to normal range respectively 0.87 nmol/L and <37 pmol/L.

Regarding the management of mammary carcinoma, chemotherapy with Lezotrole was initiated and the patient was advised to add an inhibitor of cyclin-dependent kinases Palbociclib.

Virilization and a serum total testosterone up to 5 nmol/L suggest a neoplastic source of hyperandrogenism and require further investigations [1]. The absence of either Cushing syndrome or adrenal mass suggests an ovarian testosterone production. In this case, ovarian vein sampling was not realized due to patient's

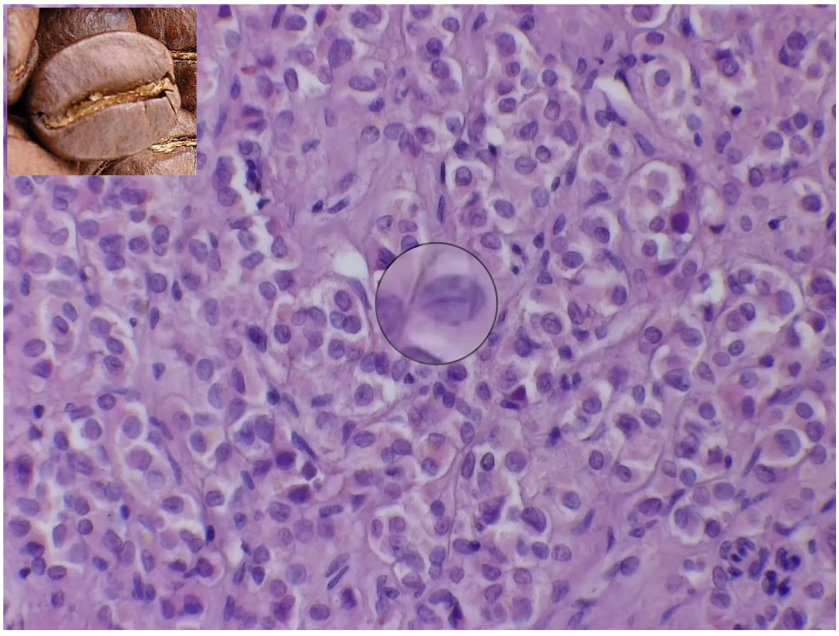

Fig. 1. Sex cord-stromal tumor with characteristic coffee bean-shaped nuclei suggesting a granulosa cell tumor.

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advanced age. Hypotheses were a small sex cord-stromal tumors, as Sertoli or Sertoli-Leydig cell tumor, or a diffuse ovarian production in the case of an ovarian hyperthecosis. Bilateral oophorectomy was consequently performed. Pathology unexpectedly revealed a granulosa cell tumor, which accounts for 2 to 5% of all ovarian malignancies [2]. Granulosa cell tumors typically present as large masses and can produce estrogen and/or progesterone whereas very rarely androgens such as testosterone [3]. We hypothesize that recurrence of the breast cancer was linked to the hyperandrogenic status due to the peripheral aromatization of excess androgens to estrogens [4]. Endometrial thickness may be linked to this phenomenon [5].

This case highlights available imaging poor performance in finding small ovarian tumor despite high secretive lesions and the need for thorough investigations following hyperandrogenism syndrome discovery.

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Declaration of Competing Interest

The authors report no conflicts of interest.

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