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Case report

Benign ovarian thecoma with markedly elevated serum inhibin B levels mimicking adult granulosa cell tumor

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ABSTRACT

Introduction: Elevated serum inhibin B is a classic marker of adult granulosa cell tumors. Here we discuss an extremely rare and informative case of elevated inhibin B associated with an ovarian thecoma.
Case: A 57 year-old postmenopausal female presented with recurrent bleeding and was found to have an adnexal mass with an elevated serum inhibin B level of 1,915 pg/mL (normal range 10–200 pg/mL). With a preoperative diagnosis of adult granulosa cell tumor, she underwent surgical management for what was ultimately a benign ovarian thecoma. The diagnosis of thecoma was confirmed by a pericellular pattern of reticulin staining and the lack of a *FOXL2* mutation by molecular testing.
Conclusion: This case demonstrates that inhibin B lacks specificity as a tumor marker for adult granulosa cell tumor, even at very high levels. Knowledge of benign alternative explanations for this finding can facilitate improved preoperative patient counseling. Pertinent literature is reviewed, with an emphasis on proposed hypotheses for inhibin overproduction.

1. Introduction

Ovarian thecomas and fibrothecomas are rare tumors of gonadal stromal cell origin, representing 3–4% of all ovarian tumors (Hugon-Rodin et al., 2016). They are benign in nature, occur predominantly in postmenopausal women and may rarely be hormonally active (Hugon-Rodin et al., 2016). There are no known associated tumor markers or consistent hormonal changes associated with thecomas, but there have been limited reported cases of associated elevated inhibin B levels, a serum marker that is classically associated with adult granulosa cell tumors. Previously reported cases of elevated inhibin B levels in the setting of ovarian thecomas have been restricted to the reproductive endocrinology literature with secondary amenorrhea and infertility as the predominant presenting complaints (Table 1).

Here, we describe the case of a postmenopausal female who initially presented with recurrent postmenopausal bleeding and was found to have an adnexal mass with markedly elevated serum inhibin B. As adult granulosa cell tumor was strongly suspected, she was counseled on a high likelihood of malignancy and she underwent surgical management. A diagnosis of thecoma was confirmed by a pericellular reticulin staining pattern and a negative result for *FOXL2* mutation by molecular testing making this (to the best of our knowledge) the fifth reported case of an ovarian thecoma with a significant serum inhibin B elevation. Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

2. Case report

Our patient, a 57 year-old postmenopausal female with a body mass index of 33, presented to clinic with a newly diagnosed adnexal mass discovered incidentally during a work up for recurrent postmenopausal bleeding. She was postmenopausal for 3 years prior to the development of uterine bleeding. A transvaginal ultrasound (TVUS) obtained by her primary gynecologist showed a thickened endometrium (20 mm), and peripheral adnexal calcifications with no definitive masses reported. She underwent hysteroscopy with dilation and curettage, which showed a

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Table 1
Summary of Cases of Elevated Inhibin B with Ovarian Thecomas. Prior cases of elevated inhibin B with ovarian thecomas have all been published in the reproductive endocrinology literature. Three cases were premenopausal women presenting with secondary amenorrhea and infertility. All cases, including the current case, had markedly elevated inhibin B levels with a normal estradiol level. Normal range for inhibin B is 10–200 pg/mL. Normal range for follicular phase estradiol level 69 to 905 pmoL/L.

	Author	Journal	Publication Year	Age	Initial presentation	Inhibin B level (pg/mL)	Estradiol (pmol/L)	Other serum hormone levels/ Tumor markers	Procedure	Frozen section	Tumor Diameter (cm)	Immunohistochemistry Stains	Final pathology
1	Meyer et al.	Fertility and Sterility	Feb. 2000	37	Secondary amennorrhea and infertility	1154	114	FSH 1.7 mIU/mL; LH 23.4 mIU/mL; normal prolactin	Diagnostic laparoscopy, chromotubation, Right ovarian cystectomy, Left ovarian excresence biopsy	Right: steroid cell tumor, no carcinoma; Left: fibro-thecomatosis vs. stromal hyperplasia	5	Strongly positive anti-Inhibin A staining. LH staining negative. Numerous psammoma bodies.	Fibrothecoma (R.) and stromal hyperplasia (L.)
2	Donovan et al.	Fertility and Sterility	Aug. 2010	20	Secondary amennorrhea and infertility	552	31	FSH 1.6 IU/L, LH 44.6 IU/L, prolactin 6 ug/L	Exploratory laparotomy, right oophorectomy	N/A	5.4	Pale elongated cells positive for inhibin alpha separated by hyalinized stroma	Thecoma
3	Van Liempt et al.	Human Reproduction	Apr. 2012	39	Secondary amenorrhea and hot flashes	553	75	CA-125 41 U/mL; CEA < 5ug/L; CA19-9 23 U/mL; BhCG < 5 U/L; AFP < 5 ug/L; Inhibin A 44 ng/L; FSH 1.9 U/L; LH 22 U/L, prolactin 0.15 U/L, Testosterone < 1.0 nmol/L, AMH 3.9 U/L	Staging laparotomy including bilateral salpingo-oophorectomy	N/A	10	Tumor positive for inhibin and negative for estrogen receptor markers. Adjacent papillary structures with seromucinous components staining negative for inhibin.	Fibrothecoma (R.), bilateral borderline seromucinous tumor
4	Hugon-Rodin et al.	Gynecologic Endocrinology	Nov. 2016	60	Referral for low FSH postmenopause in rheum work up for arthralgia	475	40	CA-125 7.8 U/mL; CEA 0.9 ug/L; HCG 4.0 UI/L, AFP < 2 ug/L; Inhibin A 100 pg/mL; FSH 6 IU/L; LH 33 IU/L; AMH < 0.3 pmol/L; Testosterone 0.33 nmol/L	total abdominal hysterectomy, bilateral salpingo-oophorectomy	N/A	11	Strongly positive anti-Inhibin A staining. Abundant collagenized bundles.	Fibrothecoma
5	Current		Oct. 2020	59	Recurrent postmenopausal bleeding	1915	63.5	CA-125 10.9 U/mL, Inhibin A 5.7, total estrogens 50.3 pg/mL, Estrone 33.0 pg/mL, Testosterone 24 ng/dL	total laparoscopic hysterectomy, bilateral salpingo-oophrectomy with removal of left adnexal mass, omental biopsy, and peritoneal washings	Favor sex cord stromal tumor with extensive luteinization	5	Special stain with reticulin is positive. Immunostains for inhibin, calretinin and smooth muscle actin are positive. Stains for desmin, beta-catenin and CD10 are negative	Ovarian thecoma, serosal endometriosis of uterus

benign endometrial polyp. She continued to have postmenopausal bleeding postoperatively and underwent repeat evaluation 7 months later. Repeat TVUS again showed a thickened endometrium, and also showed enlargement of adnexal lesions with calcifications. An endometrial biopsy was performed with benign results. At this point she was referred to our university based gynecologic oncology clinic. CT imaging of the pelvis was obtained which showed a lobulated adnexal mass containing course calcifications involving the left ovary and extending posterior to the uterus, measuring 4.5 × 3.8 × 3.1 cm. Tumor markers were obtained and were notable for a markedly elevated inhibin B of 1915 pg/mL (normal range 10–200 pg/mL). The remaining pertinent labs were all within normal limits including inhibin A (5.7 pg/mL), Ca-125 (10.9 U/mL), estradiol (17.3 pg/mL), total estrogens (50.3 pg/mL), estrone (33.0 pg/mL) and testosterone (24 ng/dL).

Given the presence of an adnexal mass and markedly elevated serum inhibin B levels, surgical management was recommended with adult granulosa cell tumor as the leading diagnosis. The patient was informed that a diagnosis of cancer was likely and was counseled on surgical management. She underwent a total laparoscopic hysterectomy and bilateral salpingo-oophorectomy with removal of left adnexal mass, an omental biopsy and peritoneal washings. Intraoperative findings were notable for an enlarged, firm, freely mobile multicystic left ovary with solid and cystic components measuring approximately 5 cm with no evidence of metastatic disease. It was removed intact with no intra-abdominal spillage of tumor. Intraoperative frozen section was reported as a luteinized sex cord-stromal tumor. No further staging was performed.

Final pathology demonstrated an ovarian thecoma of the left ovary, benign right ovary, benign fallopian tubes and uterus with endometriosis. Immunostains for inhibin, calretinin, and smooth muscle actin were all positive in the tumor. Immunostains for desmin, beta-catenin, and CD10 were negative. A reticulin stain showed a pericellular pattern of staining consistent with a thecoma (Fig. 1). Molecular testing for a *FOXL2* mutation, a sensitive and specific test for adult granulosa cell tumors, was performed and was negative.

The immunostaining, reticulin staining and molecular testing results all supported the diagnosis of an ovarian thecoma. Given her benign findings, no further treatment or surveillance was recommended.

3. Discussion

Our patient's case clinically mimics the classic presentation of an adult granulosa cell tumor—an adnexal mass accompanied by markedly elevated inhibin B levels and postmenopausal bleeding. While ovarian thecomas have been known to also be associated with postmenopausal bleeding, the novelty of this case lies in the significantly elevated serum inhibin B level observed. Inhibin B levels elevated to this extent are extremely rare for thecomas or fibrothecomas. Previous cases have been

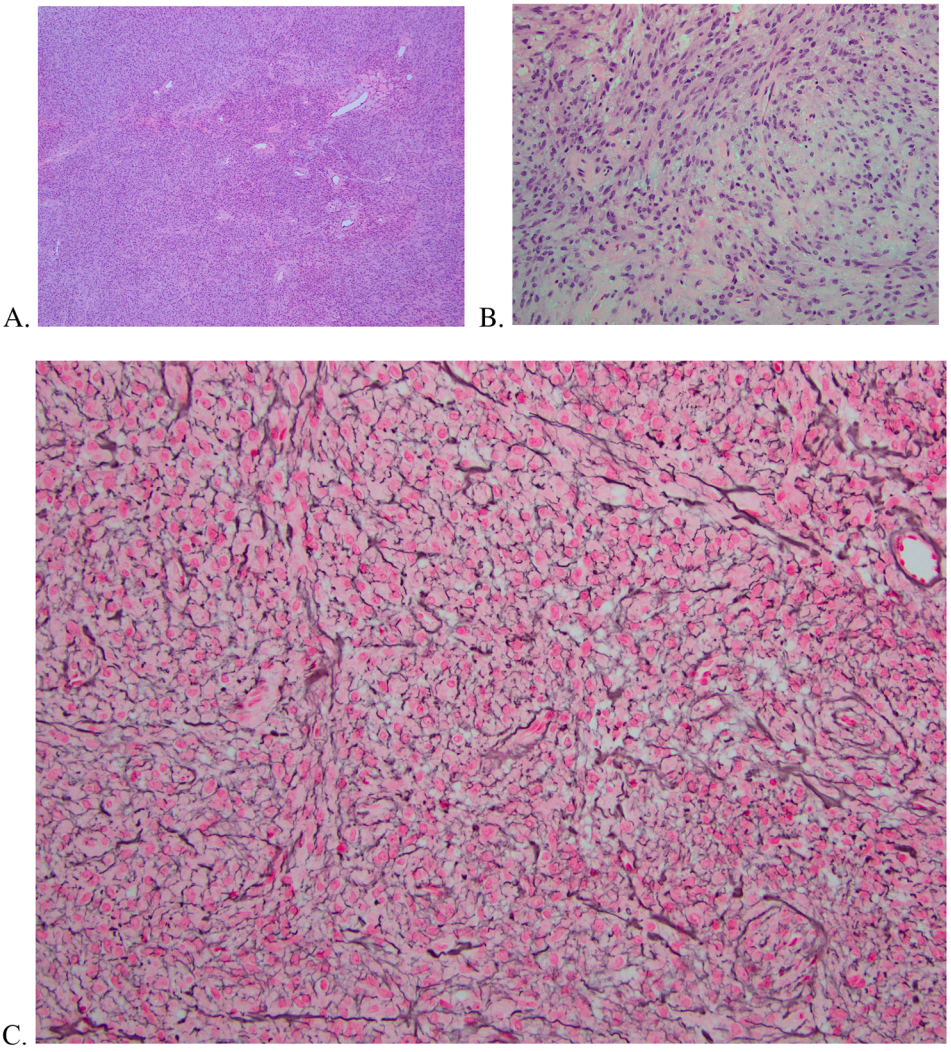

Fig. 1. Pathology. (A) Hematoxylin and eosin (H&E) stain (40×). (B) H&E stain (400×) demonstrating abundant pale cytoplasm typical of thecomas. (C) Reticulin staining (200×) showing a strong, pericellular pattern of reticulin in stark contrast to adult granulosa cell tumors, which would show loss of this pattern.

reported in the reproductive endocrinology literature (Table 1) (Hugon-Rodin et al., 2016; Meyer et al., 2000; Donovan et al., 2010; Van Liempt et al., 2012). Three of the 4 cases were premenopausal women presenting with secondary amenorrhea and infertility. All of the cases, including the one presented here, had inhibin B levels greater than twice the upper limit of normal with a normal estradiol level. By contrast, estradiol is frequently elevated in cases of adult granulosa cell tumors. Our patient's presentation differed from the previously published cases of thecomas with elevated inhibin B both based on her postmenopausal status and her vaginal bleeding (for which she had two biopsy procedures, both benign on final pathological review).

Immunohistochemistry, reticulin staining and *FOXL2* molecular testing were used to confirm the diagnosis of ovarian thecoma (Fig. 1). From a histological standpoint, it was necessary to perform this testing in order to exclude variant forms of adult granulosa cell tumor. For instance, while adult granulosa cell tumors typically have cells with scant cytoplasm, there are cases where the tumor cells are markedly luteinized and others have cells with abundant pale cytoplasm, resulting in a striking resemblance to thecomas; alternatively, some adult granulosa cell tumors can have frankly thecomatous areas, including a pericellular reticulin staining pattern (so-called granulosa theca cell tumors), again, masquerading as thecomas. In all of these tumors, the presence of a *FOXL2* mutation would confirm the diagnosis of adult granulosa cell tumor (Young, 2018; Nolan et al., 2017; Stall and Young, 2019). Thecomas show a strong, pericellular pattern of reticulin staining in stark contrast to adult granulosa cell tumors, which show loss of this pattern (Stall and Young, 2019). Increasingly, *FOXL2* mutation testing is being used for confirmation of the diagnosis of adult granulosa cell tumors. *FOXL2* is a transcription factor gene found to be mutated in 90–97% of adult granulosa cell tumors and, as such, has been identified as a sensitive and specific marker (Young, 2018; Nolan et al., 2017).

In regard to the role of imaging in preoperative diagnosis, studies have identified statistically significant differences in imaging characteristics between thecomas and other sex cord stromal tumors, namely areas of hyperintense signal density on MRI. However, imaging alone remains non-diagnostic (Li et al., 2012).

The mechanism by which a thecoma would lead to such a marked increase inhibin B is somewhat unclear. We hypothesize that the elevated inhibin B levels are the result of direct production by the proliferating theca cells, rather than via theca cell activation of granulosa cells, or as part of negative feedback cycle, but the latter remains possible (Fig. 2).

Inhibin proteins are heterodimeric glycoproteins produced by granulosa cells that result in suppression of FSH release by the anterior pituitary to down-regulate estradiol production. They share a common alpha subunit, and the beta subunit differs (denoted A or B). The majority of inhibin A is thought to be secreted by luteinized granulosa cells, whereas the majority of inhibin B is attributed to secretion by the granulosa cells of developing follicles (Hugon-Rodin et al., 2016; Namwanje and Brown, 2016). Theca cells produce androgens in response to luteinizing hormone (LH), which are then converted into estrogen by follicle stimulating hormone (FSH)-induced aromatase in neighboring granulosa cells (Young and McNeilly, 2010). This accounts for the estrogenic effects of granulosa cell tumors and the occurrence of either androgenic or estrogenic effects seen with thecomas. As part of the hypothalamic-pituitary-ovarian axis regulation, under physiologic conditions granulosa cells respond to increased estrogen levels with production of inhibin B; however, this would not explain the degree to which inhibin B was elevated in this case and others, particularly given the normal estrogen levels.

It is possible that inhibin production by thecomas is more common than previously realized, but has yet to be clinically documented. Inhibin B overproduction clinically manifests as ovulation suppression and thecomas are rare tumors occurring predominately in postmenopausal women, making this phenomenon less likely to be detected. Furthermore, there is less incentive to identify a tumor marker for a benign entity. Both granulosa cells and theca cells stain positively for the alpha inhibin subunit. Hildenbrandt et al. stained 134 ovarian tumors for inhibin, finding not only strong positivity in granulosa cells, but also 10 of 14 (71%) ovarian fibrothecomas and 17 of 18 (94%) other sex cord-stromal tumors (Hildebrandt et al., 1997). Additionally, more recent studies in have analyzed theca cell gene expression profiling by microarray analysis. While it was not part of the study aim, inhibin B RNA was isolated from theca cells during genetic analysis (Wood et al., 2005) (based on expression study data accessed via NIH GEO database). Furthermore, theca cell contribution to inhibin regulation of ovulation in regular physiology is likely comparably less than that of granulosa cells. In physiologic regulation of ovulation, it stands to reason that the proliferating and hypertrophied granulosa cells of maturing follicles would be responsible for a more clinically significant proportion of hormone production than the less robust theca interna of antral follicles, making any contribution of the latter overlooked. However, this remains speculative and further study would be necessary in order to confirm this hypothesis.

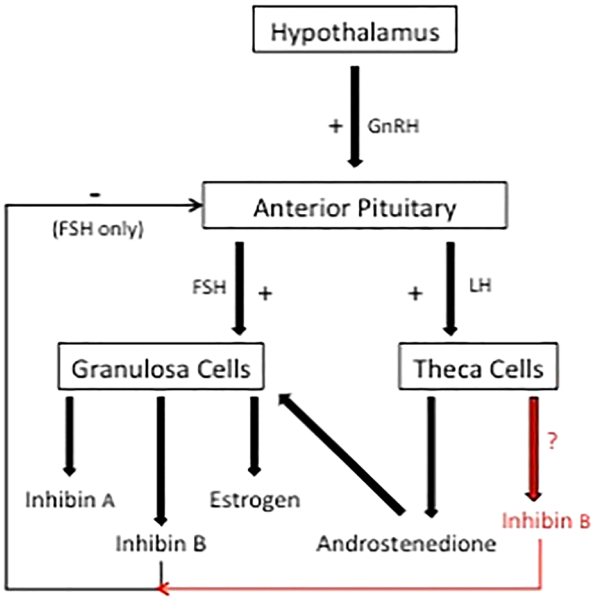

Fig. 2. Proposed mechanism of Inhibin B overproduction within the hypothalamic-pituitary-ovarian (HPO) axis. We hypothesize that the elevated inhibin B levels seen in this case are the result of direct production by the proliferating theca cells of the ovarian thecoma. The diagram above shows normal HPO axis regulation with our proposed mechanism of inhibin B production in red. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

In conclusion, while a markedly elevated serum level of inhibin B is commonly associated with adult granulosa cell tumors, it is not entirely specific for this tumor type, as illustrated by the current case. It is important that clinicians are aware that there are alternative, albeit rare, benign explanations for this finding in order to allow for optimal counseling and surgical planning.

CRediT authorship contribution statement

Erica V. Carballo: Conceptualization, Writing - original draft. **Kaley M. Gyorfi:** Writing - original draft. **Aleksandar K. Stanic:** Writing - review & editing. **Paul Weisman:** Writing - review & editing. **Christopher G. Flynn:** . **David M. Kushner:** Conceptualization, Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

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