Case report

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

Erica V. Carballo a, Kaley M. Gyorfi a, Aleksandar K. Stanic a,b, Paul Weisman c, Christopher G. Flynn c, David M. Kushner a,d,*

a University of Wisconsin, Hospitals and Clinics, Dept. of Obstetrics and Gynecology, United States
b University of Wisconsin, Division of Reproductive Endocrinology and Infertility, United States
c University of Wisconsin, Hospitals and Clinics, Dept. of Pathology and Laboratory Medicine, United States
d University of Wisconsin, Division of Gynecologic Oncology, United States

ARTICLE INFO

Keywords: Ovarian thecoma Inhibin B Tumor marker Granulosa cell tumor

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
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 amenorrhea and infertility     | 1154                    | 114               | FSH 1.7 mIU/mL; LH 23.4 mIU/mL; normal prolactin | Diagnostic laparoscopy, chromatubation, Right ovarian cystectomy, Left ovarian excrecence biopsy | Right: steroid cell tumor, no carcinoma; Left: fibrothecomatosis 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 amenorrhea and infertility     | 552                      | 31                | FSH 1.6 IU/L; LH 4.6 IU/L, prolactin 6 ug/L | Exploratory laparotomy, right oophorectomy Staging laparotomy including bilateral salpingo-oophorectomy | N/A             | 5.4                 | Pale elongated cells positive for inhibin alpha separated by hyalized 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; BkG < 5 U/L; AFP < 5 ug/l; Inhibin A 44 ng/ml; 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 U/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. Abnormal 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-oophorectomy 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. Immunoestains 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

![A. Hematoxylin and eosin (H&E) stain (40×).](image1)

![B. H&E stain (400×).](image2)

![C. Reticulin staining (200×).](image3)

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.
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 McNelly, 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 mature 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.

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

References

Donovan, L.E., Brain, P.H., Duggan, M.A., 2010. Isolated luteinizing hormone (LH) elevation in a woman with secondary amenorrhea: A clue to the diagnosis of an inhibin B-producing thecoma and insights into the influence of inhibin B on LH. Fertil. Steril. 94 (3), 1097.e9–1097.e12. https://doi.org/10.1016/j.fertnstert.2010.02.016.

Hildebrandt, R.H., Rouse, R.V., Longacre, T.A., 1997. Value of inhibin in the identification of granulosa cell tumors of the ovary. Hum. Pathol. 28 (12), 1387-1395. https://doi.org/10.1016/S0046-8177(97)90229-X.

Hugon-Rodin, J., Kalhorpour, N., Borghese, B., et al., 2016. Inhibin A and inhibin B producing ovarian fibrothecoma revealed by suppression of follicle stimulating hormone (FSH) in a post-menopausal woman: report of the first case. Gynecol. Endocrinol. 32 (11), 872-874. https://doi.org/10.1080/09513590.2016.1222364.

Li, X., Zhang, W., Zhu, G., Sun, C., Liu, Q., Shen, Y., 2012. Imaging features and pathologic characteristics of ovarian thecoma. J. Comput. Assist Tomogr. 36 (1), 46-53. https://doi.org/10.1097/RCT.0b013e3182386186.

Meyer, A.C., Papadimitriou, J.C., Silverberg, S.G., Sharara, F.I., 2000. Secondary amenorrhea and infertility caused by an inhibin-B-producing ovarian fibrothecoma. Fertil. Steril. 73 (2), 258-260. https://doi.org/10.1016/S0016-0282(99)00511-7.

Van Liempt, S.W.J.D., Van Rheenen-Flach, L.E., Van Waesberghe, J.H.T.M., Bleeker, M.C.G., Piek, J.M.J., Lambalk, C.B., 2012. Solely inhibin B producing ovarian tumour as a cause of secondary amenorrhoea with hot flushes: case report and review of literature. Hum. Reprod. 27 (4), 1144-1148. https://doi.org/10.1093/humrep/der475.

Wood, J.R., Nelson-Degrave, V.L., Jansen, E., McAllister, J.M., Mosselman, S., Strauss, J. F., 2005. Valproate-induced alterations in human theca cell gene expression: Clues to the association between valproate use and metabolic side effects. Physiol. Genom. 20, 233-243. https://doi.org/10.1152/physiolgenomics.00193.2004.

Young, R.H., 2018. Ovarian sex cord-stromal tumours and their mimics. Pathology 50 (1), 5-15. https://doi.org/10.1016/j.pathol.2017.09.007.

Young, J.M., McNeilly, A.S., 2010. Theca: The forgotten cell of the ovarian follicle. Reproduction 140 (4), 489-504. https://doi.org/10.1530/REP-10-0094.