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# Increased Serum Inhibin Associated with Ovarian Fibroma Neoplasms

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## Abstract

**Background:** Clinicians are commonly tasked to evaluate adnexal masses. Both radiography and serum markers are useful in the counseling of patients regarding management options. Inhibin is one of several tumor markers used in the evaluation of adnexal masses given its known association with sex cord stromal tumors, specifically granulosa cell tumors.

**Case 1:** 68 year old G6P6 Caucasian female who initially presented to her provider with post-menopausal bleeding; work up demonstrated a complex adnexal mass and a serum Inhibin B level of 277 (normal < 10). She underwent a hysterectomy and bilateral salpingo-oophorectomy with final pathology returning as a benign fibroma.

**Case 2:** 38 year old G2P1011 African American female who presented to the emergency department for abdominal pain; a pelvic ultrasound demonstrated a complex left adnexal mass. Serum tumor markers included an Inhibin B of 719 (normal <139). An ovarian cystectomy was performed and pathology returned as a cystadenofibroma.

**Discussion:** In these two patients, granulosa cell tumor was suspected initially as both had markedly elevated inhibin B levels in the setting of an adnexal mass. Both patients were counseled on the need for surgery and possibility of surgical staging. However, for each patient, frozen section demonstrated benign fibromas. In Case 2, we were able to preserve ovarian tissue given the desire for future fertility. Both cases demonstrate that while tumor markers can be helpful in providing additional information in the evaluation of adnexal masses, they are not diagnostic tests and surgical management is the only means for a diagnosis.

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## Introduction

Adnexal masses are common; in fact, 5-10% of women undergo surgery for an adnexal mass in their lifetime [1]. In the primary evaluation of an adnexal mass, radiographic appearance and tumor markers may assist the clinician in determining a possible diagnosis. Radiographic appearance characterizes adnexal masses – size, complexity of the mass, and the presence of ascites should be noted for assistance management strategy – surgery or observation [2] and preferred provider–general gynecologist or gynecologic oncologist. Tumor markers and family history can be a helpful adjunct in management decisions. While there is no tumor marker that is sensitive or specific enough to be used as a screening tool, often case-specific clinical information and characteristics of the adnexal mass can help guide clinicians as to which serum tumor marker(s) may be clinically useful [3].

Tumor markers differ based on cell type and multiple serum tumor markers are used for assessing adnexal pathology [4]. Inhibin is a tumor marker associated with sex cord stromal tumors, specifically granulosa cell tumors. These tumors may also produce estradiol, which often correlates with the symptoms of hyperestrogenism, including abnormal uterine bleeding, and may also be associated with endometrial cancer [5,6].

## Case 1

68 year old G6P6 Caucasian female who presented to her provider with a 10 day history of light post-menopausal vaginal bleeding, the patient denied bladder or bowel issues, weight loss, and abdominal pain or bloating. Her past medical history included well controlled hypertension. She had a remote history of an abnormal pap smear. She had been menopausal since the age of 48 and menarche was age 14. Her obstetrical history included six vaginal deliveries. Surgical history was non-contributory. Her family history included a sister with breast cancer and a brother with esophageal cancer.

**Table 1:** Cases with elevated inhibin or inhibin immunostaining in benign pathologies.

| Table | Pathology | Inhibin related findings |
|---|---|---|
| Meyer et al. [13] | Case report of Fibrothecoma | Elevated Inhibin B with positive inhibin immunostaining |
| Van et al. [10] | Case report of Fibrothecoma | Elevated Inhibin B with positive inhibin immunostaining |
| Donovan et al. [7] | Case report of Thecoma | Elevated Inhibin B with positive inhibin immunostaining |
| Hildebrandt et al. [27] | 10/14 (71%) Fibrothecomas | Inhibin staining present |
| Flemming et al. [28] | 10/10 ( 100%) Fibrothecomas | Positive for inhibin |
| Flemming et al. [28] | 4/6 (67%) Thecomas | Inhibin staining positive |
| Robertson and McNeilage [9] | 4/4 (100%) Thecomas | Elevated serum inhibin |
| Healy et al. [20] | 3/4 (75%) Fibromas, 4/4 (100%) Thecomas | Elevated serum inhibin concentration |

A gynecological exam included a normal vagina and cervix on speculum exam, uterus was normal shape and size on bimanual. Her adnexa on bimanual and rectovaginal examinations were noted to have fullness on the left side, there was no cul de sac nodularity noted. A pelvic ultrasound demonstrated a thickened endometrial lining (13.8 mm, normal <4 mm) and a complex left adnexal mass (7 x 5.3 x 5.9 cm). An endometrial biopsy was performed that was negative for malignancy or hyperplasia. Serum tumor markers were obtained and demonstrated an elevated Ca-125 (63.7, normal <35), elevated Inhibin B (277, normal < 10) and mildly elevated Inhibin A (7.7, normal < 6.9).

She underwent a total abdominal hysterectomy, bilateral salpingo-oophorectomy with an intra-operative frozen section. Frozen section was consistent with an ovarian stromal tumor favoring fibroma and final pathology confirmed the diagnosis. Pathological exam included an 8.8 x 5.6 x 5.4 cm ovarian mass focally multinodular external appearance with whorled rubbery tissue and no hemorrhage or necrosis. No immunohistochemical testing was performed given the histological appearance of the specimen (Table 1).

No further treatment was required. Four months post-op the patient had repeat Ca -125 and Inhibin B levels tested both of which had normalized 5 and <10, respectively.

## Case 2

38 year old G2P1011 African American female who presented to the emergency department with a two day history of left sided abdominal pain – she had an ultrasound performed and was discharged with referral to gynecology. The pelvic ultrasound demonstrated a complex left adnexal mass (7.8 x 8.1 x 8.5 cm).

The patient had a past medical history of well controlled hypertension and obesity. Her surgical history included a right salpingo-oophorectomy for an ectopic pregnancy. Her mother was reported to have a questionable history of a gynecological malignancy. She had a history of a vaginal delivery and no other gynecological or obstetrical issues. She underwent menarche at the age of 9.

At her follow up appointment with gynecology her previous records were reviewed and it was noted that this adnexal mass had been present and stable for the last 3 years. The patient desired future fertility and had concerns about the possibility of losing her remaining ovary. She denied bladder or bowel issues and abnormal uterine bleeding but did note she had lost about 10 pounds over the preceding couple of months. Her gynecological exam demonstrated a normal vagina and cervix on speculum exam. Her bimanual was limited given her habitus but no abnormalities were appreciated. Tumor markers collected 3 years prior were normal. Follow up tumor markers collected demonstrated a normal Alpha-Fetal-Protein (AFP) (1.8, normal <8.5), normal Ca-125 (14, normal <35), normal Ca 19-9 (31, normal <37), normal Inhibin A (6.8, normal <97) and a markedly elevated Inhibin B (719, normal <139). Given the elevated Inhibin B levels in conjunction with an adnexal mass, the concern for a granulosa cell tumor was discussed with the patient. Given her desired fertility, an ovarian cystectomy was discussed with the plan for a completion oophorectomy and surgical staging if a malignancy was found. A cystectomy was performed with frozen section consistent with serous cystadenofibroma which was confirmed on final pathology. The cyst was to be 9.8 x 7.9 x 6.7 cm and upon sectioning no areas of nodular induration or papillary excrescences were identified. No immunohistochemical testing was performed given the histologic appearance of the specimen.

No further therapy was required and the patient did not have a follow up Inhibin drawn.

## Discussion

### Sex cord stromal tumors

Sex cord stromal tumors (SCST) are a heterogeneous group of tumors originating from the ovarian stroma surrounding oocytes. They make up a variety of benign and malignant tumors [7]. SCST compose 8% of all ovarian tumors and include granulosa, Sertoli-Leydig, theca, nonspecific gonadal stromal cell, and single or mixed types of tumors [8-10]. SCST are also heterogeneous in their ability to produce steroids or other hormones [11].

As previously mentioned, the hormone (specifically inhibin B) producing capacity of GCT has already been established [12]. GCT are typically steroidogenic, secreting estrogen in supra-physiologic amounts 70% of the time. Granulosa cell tumors are the most common of the malignant SCST, accounting for 5-10% of all ovarian malignancies [8,13,14].

Sex cord stromal tumors composed of pure ovarian stroma are typically solid benign tumors, and over 50% are fibromas [11]. Ovarian fibromas and fibrothecomas are uncommon, accounting for only 1-5% of ovarian tumors [15-17]. The risk of malignancy with a solid ovarian tumor is 8.7%, therefore, surgical removal of all solid ovarian tumors is universally recommended [18].

### Inhibin as a tumor marker

Inhibin is a tumor marker for gynecologic malignancy, often elevated in both granulosa cell tumors (GCT) and mucinous cystadenocarcinomas [8,19,20]. As a tumor marker for GCT, inhibin is thought to be reliable as levels decrease following surgery, increase with recurrence, and magnitude directly correlates with tumor size [11,21,22]. Inhibin is a less reliable ovarian tumor marker in

premenopausal women, as inhibin levels vary with the menstrual cycle, reflecting the varying levels of FSH [23,24]. Inhibin peaks mid-cycle and during the luteal phase, at which time levels are high enough to make it difficult to detect potential excess inhibin production from a tumor [9]. In postmenopausal and surgically castrated women, inhibin levels are normally undetectable since the ovarian tissue is less functional in the production of estrogen in these two patient populations, making it a more reliable tumor marker in those clinical situations [25]. The primary source of inhibin production in the non-pregnant woman is the ovary [26]. Other minor sites of inhibin production include the pituitary, adrenal gland, and the placenta during pregnancy [13].

## Conclusion

Adnexal masses are a common source of referral for gynecological oncologists. The use of serum tumor markers assists physicians in counseling and operative planning in these patients. Tumor markers are additionally useful in following response to treatment. In the counseling of patients with adnexal masses and elevated inhibin levels the risk of a granulosa cell malignancy must discussed. Patients at risk for malignancy should receive pre-operative counseling that comprehensive surgical staging may be indicated. Patients must also be counseled that if malignancy is encountered adjuvant therapy with chemotherapy may be indicated. Patients must also be counseled that while suspicion may be high for malignancy that the diagnosis can only be made after surgery and that a benign inhibin secreting adnexal mass is possible.

In these two patients, the diagnosis of granulosa cell tumor was suspected initially as both had markedly elevated inhibin B levels in the setting of an adnexal mass. In Case 1, the patient additionally had symptoms that could be attributable to hyperestrogenism. Both patients were counseled on the need for surgery and possibility of surgical staging. However, for each patient, frozen section demonstrated benign fibromas. In Case 2, we were able to preserve ovarian tissue given the desire for future fertility. Both cases demonstrate that while tumor markers can be helpful in providing additional information in the evaluation of adnexal masses, they are not diagnostic tests and surgical management is the only means for a diagnosis. Fertility sparing surgery may be acceptable when an ovarian cystectomy can be performed and a frozen section is benign in select cases. In cases which an ovarian cystectomy is decided upon the surgeon must exercise caution to avoid cyst rupture as to not seed the abdomen with potential malignancy if pathology demonstrates a malignant process. Continued following of serum markers after benign pathology is not usually necessary, but there should be some consideration to following laboratory evaluation in patients with ovarian cystectomy and ovarian preservation. The prognosis of adnexal masses will depend on the pathological diagnosis and not the elevation of inhibin.

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