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CASE REPORT

Inhibin B Secreting Ovarian Fibroma

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Abstract

Background Nearly 90% of all the hormone-producing ovarian tumours are sex cord-stromal tumours (SCSTs). The Ovarian fibroma is a hormonally inactive variant of SCST. It is composed of spindle, oval, round cells producing collagen and accounts for approximately 4% of all ovarian neoplasms. Amongst the other SCSTs, Inhibin B is an important tumour marker. It is a heterodimeric glycoprotein hormone that is secreted primarily by the granulosa cells of the developing follicles. High levels of Inhibin-B can hamper follicular recruitment, leading to amenorrhea in a reproductive age woman.

Finding In this case report, we describe a rare case of a reproductive age female presenting with secondary amenorrhea, having an Ovarian Fibroma, producing massive amounts of Inhibin B.

Significance Although some pathological variants of ovarian fibromas like cyst-adeno-fibroma and ovarian fibro-thecoma are known to secrete inhibin B, benign /pure ovarian fibromas rarely do so.

Keywords Ovarian fibroma · Inhibin B · Secondary amenorrhea · FSH

Case Report

A 38 years old, multiparous woman, known case of hypothyroidism, came with the chief complaint of amenorrhea and weight gain for 3 years. She was investigated in the department of endocrinology and surgery, where she was advised to undergo serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid function test (TFT's), Prolactin hormone measurements, and ultrasound pelvis. Her FSH levels were found low and pelvic scan was suggestive of a retroperitoneal mass. The origin and nature of the mass was confirmed on contrast-enhanced computed tomography (CECT) abdomen and pelvis, on which a well-defined homogenously enhancing left adnexal solid mass lesion of size $11.0 \times 14.1 \times 13.4$ cm with persistent delayed enhancement was seen and the left ovary could not be separately visualised. Impression of an ovarian mass likely to be an ovarian fibroma or fibro-thecoma was made and the patient was referred to gynaecology department, where she was evaluated, on lines of hypogonadotropic hypogonadism as the cause of premature menopause and its relation with the ovarian mass (if at all present). She had no history s/o space-occupying lesion in the brain, hyperandrogenism, hypothalamic cause of amenorrhea. History of significant weight gain could not be explained by hypothyroidism as she was controlled on Tab. thyroxine 150mcg BBF (compliant). She attained menarche at 13yrs of age and had regular cycles, prior to attaining menopause 3yrs back. Family history was not significant.

She was morbidly obese (BMI—42 kg/ m2). A mobile, firm mass of 18 weeks size with regular margins was palpable in the left iliac fossa. The same mass was felt per vaginally deviating the uterus backward.

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Table 1 Pre-operative Tumour markers and hormone levels: (as on 28th December,2019)

Tumour marker and hormones	Levels
INHIBIN B	**> 1300 pg./ml (high)**
Alpha Feto Protein	4.29 ng/ml
Beta HCG	3.35mIU/mL
CA 125	6.24U/ml
LDH	197mIU/L
Prolactin	4.15 ng/ml
FSH	**1.88mIU/ml (low)**
Testosterone	13.32 ng/dl

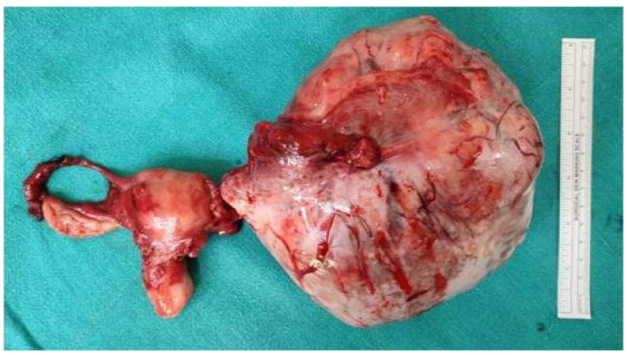

Fig. 1 An ovarian mass of size13 × 12x7cm with an intact capsule, smooth lobulated surface, along with left fallopian tube stretched over it. Picture also depicts the normal looking uterus and right fallopian tube and ovary

She was advised tumour markers evaluation, amongst which Inhibin B was markedly raised (> 1300 pg./ml) [Table 1].

Provisional Diagnosis of premature menopause in 38yrs, multiparous hypothyroid female with ovarian mass? Inhibin B secreting SCST (more likely an ovarian fibro-thecoma or granulosa cell tumour) was made and patient planned for surgery.

Patient was given 2 surgical options:- First was laparotomy followed by unilateral salpingo-oophorectomy and frozen section to identify the nature of the mass (benign or malignant), followed by Hysterectomy with contralateral salpingo-oophorectomy and omentectomy if malignancy was proven on frozen section. Second was hysterectomy with bilateral salpingo-oophorectomy (BSO) ± omentectomy. Two different SCSTs could co-exist in either of the ovaries, or, the normal looking right ovary (on CECT) could also be the probable source of raised Inhibin B. So, the option of doing BSO irrespective of the frozen section report, was given and side effects of BSO (premature menopause and the need for postoperative hormone therapy) were explained to the patient). Patient opted for hysterectomy

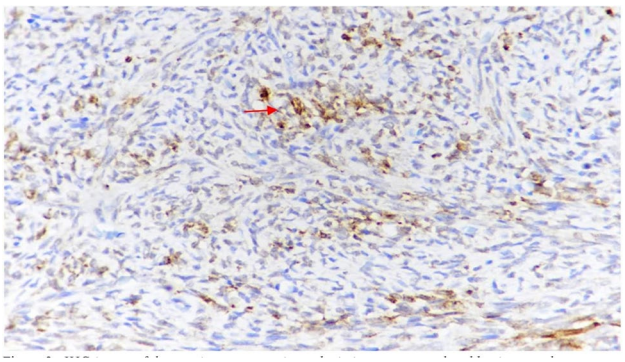

Fig. 2 IHC image of the ovarian mass specimen depicting an encapsulated benign neoplasm comprising of spindle-shaped cells arranged in long fascicles and forming whorls at places, s/o ovarian fibroma. The spindle-shaped cells showed variable expression for Inhibin B (red arrow; brown colour) and were immune-negative for Caldesmon (thus, the smooth muscle nature of the neoplasm ruled out)

with BSO. She underwent an exploratory laparotomy followed by left ovarian mass excision [Fig. 1—ovarian mass of size13 × 12x7cm with an intact capsule, smooth lobulated surface, along with left fallopian tube stretched over it]. It was sent for frozen section which was reported as ovarian fibroma. But, malignancy could be completely ruled out only on final histopathology report. So, a total abdominal hysterectomy (normal looking uterus with cervix intraoperatively) with right salpingo-oophorectomy (right tube and ovary normal looking) was done, as decided preoperatively [Figure 1]. Retroperitoneal lymph node dissection was not done as the mass was thought to be either benign or a granulosa – stromal cell tumour. Peritoneal Fluid washing was sent for cytology testing—No atypical or malignant cells were detected.

The patient was started on low-molecular-weight heparin for thromboprophylaxis (i.v.o. morbid obesity) and was discharged on day 4 of surgery.

The patient followed up after 2 weeks with the HPE report that revealed a normal right ovarian tissue and a left ovarian mass showing, an encapsulated benign neoplasm comprising of spindle-shaped cells arranged in long fascicles and forming whorls at places, s/o ovarian fibroma. Tumour cells were relatively monomorphic with a spindle to elongated nuclei, bland chromatin, and inconspicuous nucleoli and had a moderate amount of pale eosinophilic cytoplasm; areas of collagenisation seen. Mitoses seen was 2/10 high power field with no appreciable nuclear atypia. No evidence of malignancy, necrosis, calcification.

Uterus with cervix- unremarkable.

To confirm the source of raised Inhibin -B and to rule out the presence of theca cells in the tumour, immunohistochemical staining was done. On IHC, [Fig. 2] the spindle-shaped cells showed variable expression for Inhibin B and were

Table 2 Levels of Inhibin B in various conditions causing secondary amenorrhea

Conditions leading to secondary amenorrhea	INHIBIN B
Hypothalamic amenorrhea	Normal
Premature Ovarian Failure	Low
Sex Cord Stromal Tumours [5]: -Granulosa Cell Tumour Thecoma Ovarian Fibro-thecoma Ovarian cystadenofibroma Sertoli/ Leydig cell tumours	RAISED

immune-negative for Caldesmon (thus, the smooth muscle nature of the neoplasm ruled out). Postoperative Inhibin B levels were normal (0.57 pg/ml). Hence, the final Diagnosis of Inhibin –B secreting Ovarian Fibroma was made and the benign nature of the disease was explained to the patient. She was advised to continue anticoagulation for 28 days and has been asked to follow up after 6 months.

Discussion

Secondary amenorrhea is the absence of menstruation in women who previously had normal menstrual cycles. The most common cause of secondary amenorrhea in a reproductive age woman is pregnancy. Other causes are depicted in PCOS, endocrine disorders (like hypothyroidism or hyperprolactinemia), Premature ovarian failure (POI) and Hypothalamic amenorrhea. WHO has classified causes of amenorrhea into 3 major groups; normogonadotropic normogonadism (e.g., PCOS), hypergonadotropic hypogonadism (e.g., POI) and Hypogonadotropic hypogonadism which is characterised by low FSH due to decreased synthesis (either because of abnormality in the hypothalamus and pituitary or because of inhibition by raised levels of inhibin B). Raised Inhibin B levels caused amenorrhea in our patient, which is quite a rare scenario. Inhibin are heterodimeric glycoprotein hormones composed of a common A and distinct B-subunits [1]. Two forms of inhibin have been purified, inhibin A and inhibin B. Gonadal inhibin is produced in the granulosa cells (ovary) and the Sertoli cells (testis). Other sites of inhibin production are: pituitary, adrenal, placenta, and corpus luteum. Inhibin-A appears to be secreted primarily by the corpus luteum, and Inhibin B is secreted primarily by the granulosa cells of the developing follicles. Elevated levels of Inhibin B in reproductive-aged women could lead to ovulatory dysfunction by inhibiting follicular recruitment, leading to amenorrhea (as in this case). Usually, such high levels of Inhibin B are found in cases of SCSTs particularly granulosa cell tumours [Table 2] which generally present with heavy menstrual bleed instead of amenorrhea.

On the other hand, ovarian fibromas are hormonally inactive variants of SCSTs [2]. Inhibin B or other tumour markers thus have nearly no role in its diagnosis or prognosis. Ovarian fibromas, the most common benign solid tumours of the ovary (constituting ~ 4% of all ovarian tumours [3]), are composed of spindle-shaped cells that produce collagen. Our case is unique, as in our patient, this tumour that is known to be hormonally inactive, produced massive amounts of Inhibin B(> 1300 pg/ml), which was confirmed on IHC and by postoperative fall of Inhibin B levels. Raised Inhibin B caused secondary amenorrhea (the primary symptom of our patient). Also, to note, all the cases of Inhibin B secreting ovarian tumours that have been reported so far, are of other SCSTs (Table 2). The Theca cells in fibro-thecomas can be considered responsible for the secretion of Inhibin B. But in our case, the absence of theca cells makes it a rare case of an ovarian fibroma secreting Inhibin B.

Women with secondary amenorrhea and ovarian neoplasms must always undergo Inhibin assessment and surgery must be planned as for any other malignant granulosa-stromal cell tumour as nearly 90% of all the hormone-producing ovarian tumours are sex cord-stromal tumours (SCSTs) [4].

Frozen Section testing in women willing for fertility preservation can save the complications of a more morbid surgery and repeated follow up.

Post-operative tumour markers must be measured to document the fall that ensures the source and has a prognostic role in the follow up of malignant tumours.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed during the treatment of the concerned patient were in accordance with the ethical standards of AIIMS.

Informed Consent Informed consent was obtained from the patient.

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