Clinical case

Isolated FSH deficiency revealing a granulosa cell tumor

Déficit isolé de la FSH révélateur d’une tumeur de la granulosa

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Résumé
Nous rapportons l’observation d’une patiente de 41 ans consultant pour aménorrhée secondaire récente et infertilité. Le bilan initial éliminait une insuffisance ovarienne, un syndrome des ovaires polykystiques et orientait vers une origine hypothalamo-hypophysaire. Cependant, le profil hormonal inhabituel avec FSH effondrée, LH normale et estradiol dosable, associé à un test à la progestérone positif nous a fait rechercher l’existence d’un facteur freinateur de la FSH : le taux d’inhibine B plasmatique très élevé et les examens morphologiques nous ont orientés vers une tumeur ovarienne de la granulosa. Le taux d’AMH était également élevé. La chirurgie et l’anatomopathologie sont venues confirmer ce diagnostic. Cette observation récente, explorée avec les moyens actuels, a pour intérêt de montrer à la fois le profil hormonal et son évolution ainsi qu’une imagerie complète.

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Mots clés : Aménorrhée ; Inhibine B ; Hormone antimmullérienne ; Tumeur à cellules de la granulosa ; Déficit FSH

Abstract
We report a case of a 41-year-old woman with a recent secondary amenorrhea and infertility. The initial assessment ruled out premature ovarian failure, polycystic ovary syndrome and led to suspect a hypothalamo-pituitary cause. However, the unusual hormone pattern with a very low level of FSH, normal levels of LH and estradiol, associated with a positive progesterone test suggested the presence of a FSH inhibiting factor: the unexpectedly high levels of inhibin B and AMH were suggestive of a granulosa cell tumor as showed by the radiologic findings. This prompted a surgical exploration, which confirmed the putative diagnosis. This case report illustrates the inhibin B and AMH values and the modern-day pelvic imaging data encountered in menstrual irregularities caused by a granulosa cell tumor.

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Keywords: Amenorrhea; Inhibin; Antimullerian hormone; Granulosa cell tumor; FSH deficit

1. Introduction

Secondary amenorrhea is a common reason for consultations in the Endocrinology Department, the main causes in order of frequency being polycystic ovary syndrome, hypothalamic amenorrhea, hyperprolactinaemia and ovarian failure [1]; ovarian tumors remain exceptional etiologies, but the related challenges in prognosis means that they must not be underestimated.

Ovarian granulosa cell tumors represent 2 to 5% of all ovarian cancers; their prognosis is good on the whole, but recurrences can be slow, sometimes 20 to 30 years after their initial diagnosis [2]. These tumors are most often the cause of a hypersecretion of ovarian peptides, the classic ovarian tumor markers (CA 125, ACE) often being unaffected [3].

Here, we present the case of a patient with an ovarian granulosa cell tumor secreting inhibin B and AMH, who sought care...
for secondary infertility with oligomenorrhea and then amenorrhea.

The purpose of this report is to demonstrate the full imaging findings (ultrasound, MRI and pathology imaging) of the ovarian tumor and the pre- and postoperative hormonal profile, in particular the gonadotrophins and ovarian peptides.

2. Observation

A patient aged 41, gravida 2, para 0, was referred by her attending physician for induced ovulation via GnRH pump as a treatment for infertility and amenorrhea. Tests carried out during a period of amenorrhea showed a normal LH at 3.7 IU/l and a drastically reduced FSH at 0.1 IU/l.

The patient’s cycles had always been regular up to her last pregnancy, at the age of 36, which ended in a miscarriage. She then developed oligomenorrhea bordering on amenorrhea, which ended following a course of progesterone for several cycles.

She was not taking any medication.

Clinically, her BMI was 37, with no signs of hyperandrogenism, galactorrhea or stretch marks. The gynecological examination was normal; a cervical smear was obtained.

The GnRH test (Table 1) showed a drastically reduced and non-stimulable FSH and a normal, moderately reactive LH. Estradiol was 156 pg/ml; plasma androgen and prolactin levels were normal.

As the FSH, LH and estradiol values were not compatible with the hypothalamic-pituitary origin initially suspected, we examined the possibility of an FSH inhibiting factor: inhibin B was found to be at a very high level at 3299 pg/ml (N: 45 to 200 pg/ml, ELISA method), inhibin A was undetectable. The AMH level (119 ng/ml, n < 6) was also very high. These two markers were highly suggestive of a granulosa cell tumor; the other biological tumor markers (ACE, CA 125, LDH) were normal.

The pelvic ultrasound showed an 8-cm mixed latero-uterine image on the left; the other ovary was small; the endometrium was not hypertrophic (Fig. 1).

The absence of nodal enlargement associated with the mixed-mass syndrome was confirmed on the pelvic MRI (Fig. 2).

No endometrial hypertrophy was found, despite the hyperoestrogenism, probably as a result of the prior course of progestagen treatment.

Bearing in mind the patient’s desire for pregnancy, left adnexectomy was carried out, preserving the right ovary. The pathology study revealed a 9-cm ovarian granulosa cell tumor spreading through the capsule, not the tubes, with no vascular embolus (Fig. 3); the cytology study of the peritoneal fluid contained tumor cells.

Postoperatively, the cycles were reestablished, inhibin B was low and FSH returned to normal (Table 1).

The tumor stage was 1c and additional surgery (contralateral adnexectomy, complete hysterectomy, infragastric omentectomy, multiple peritoneal biopsies and peritoneal cytology) was performed; no tumor extension was found.

Additional chemotherapy (BEP protocol: bleomycin, etoposide and cisplatin) was started.

3. Discussion

Amenorrhea of hypothalamic origin is a classic cause of secondary amenorrhea. This diagnosis was initially suspected in the present case on the basis of the FSH values. However, the isolated nature of the drop in FSH with normal LH levels does not fit the usual hormonal profile for this type of amenorrhea; in this situation, LH is usually lower than FSH or the two gonadotrophins are clearly reduced [4].

Mutations in the subunit β can be the cause of an isolated FSH deficit [5]. The clinical presentation for this rare mutation is completely different from that presented by our patient, whose amenorrhea was recent.

Table 1
Baseline and postoperative hormonal assays.

<table>
<thead>
<tr>
<th></th>
<th>Estradiol pg/ml</th>
<th>FSH (t0) IU/L</th>
<th>FSH (t120) IU/L</th>
<th>LH (t0) IU/L</th>
<th>LH (t120) IU/L</th>
<th>Inhibin B pg/ml</th>
<th>AMH ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>156</td>
<td>0.2</td>
<td>0.3</td>
<td>2.1</td>
<td>5.9</td>
<td>3299</td>
<td>119</td>
</tr>
<tr>
<td>Postoperativeb</td>
<td>34</td>
<td>6.5</td>
<td>7.9</td>
<td>3.7</td>
<td>6.9</td>
<td>18</td>
<td>0.69</td>
</tr>
</tbody>
</table>

a t0 and t120 min GnRH test (100 μg) values.
b Post-operative values 1 month after left adnexectomy.
Fig. 2. 3Tesla T2 (a) and fat suppressed gadolinium-enhanced T1-weighted (b) magnetic resonance axial images. A well-limited 9 × 4 × 8 cm large left ovarian mass is seen. This mass is ovoid, and contains a multilocular cystic component displaying high signal intensity on T2-weighted images (arrow) and an enhancing tissue component (arrowhead).

As reported by Krishan et al. in 2003, ultrasound and hormonal abnormalities that are less typical than those of our patient can be confused with polycystic ovary syndrome [6]. The following elements may in fact suggest a diagnosis of PCOS: increased LH/FSH ratio, positive progesterone test; however, the changing history, the ultrasound appearance and the particularly low FSH value generally allow the difference to be made.

Table 2
Hormonal profile and immunohistochemical staining: review of the recent literature.

<table>
<thead>
<tr>
<th>Authors and year</th>
<th>Age</th>
<th>LH IU/L</th>
<th>FSH IU/L</th>
<th>Estradiol g/ml</th>
<th>Inhibin B g/ml</th>
<th>AMH g/ml</th>
<th>IHC staining for inhibin α</th>
<th>IHC staining for inhibin β</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krishnan et al. [6] 2003</td>
<td>36</td>
<td>6.7</td>
<td>0.8</td>
<td>129</td>
<td>147</td>
<td></td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Kurihara et al. [12] 2003</td>
<td>31</td>
<td>9.8</td>
<td>0.3</td>
<td>142</td>
<td>2429</td>
<td></td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Agha-Hosseini et al. [17] 2009</td>
<td>26</td>
<td>1.4</td>
<td>0.1</td>
<td>100</td>
<td>1124</td>
<td></td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>Our case report 2009</td>
<td>41</td>
<td>2.1</td>
<td>0.2</td>
<td>156</td>
<td>3299</td>
<td>119</td>
<td>Positive</td>
<td></td>
</tr>
</tbody>
</table>

Inhibins are glycoproteins secreted by the granulosa cells during the menstrual cycle, which are now well known to have a specific inhibiting effect on FSH [7]. In contrast, raised FSH levels are present in patients with low inhibin B levels (natural menopause or ovarian failure after chemotherapy, for example) [8].

Inhibins A and B are formed from two subunits: α, common to both forms and β, which is specific. These peptides are also potential markers for ovarian granulosa cell tumors [7,9]: inhibin A is secreted in large quantities in juvenile tumors, but more rarely in its adult form, whereas inhibin B is produced in excess in both forms [8,10,11].

The existence of inhibin B hypersecretion is highlighted in the case. Inhibin A was undetectable.

Immunohistochemical staining of the tumor was positive for inhibin α, as already described by Kurihara et al. [12], whereas it was positive for the β fraction for Krishnan et al. [6].

In the literature, we have found several similar clinical cases with this particular hormonal profile (Table 2), which the authors have described as a pseudo-FSH deficiency [6,13].

Older studies [9,14,15], not listed in Table 2, showed hormonal profiles that were similar but less homogeneous, especially in the inhibin measurement, which was not selective for the two forms, thus not allowing a precise comparison with our case.

Physiologically, selective FSH inhibition is mainly caused by the effect of the inhibin, but also by that of estradiol [16]. In granulosa cell tumors, the secretion of inhibins is more often very high, whereas estradiol secretion is only moderate (Table 2).

Sakamoto et al. reported a case with low estradiol and a clearly lowered FSH level, pointing out the major role played by inhibin in reducing FSH [15].

Agha-Hosseini et al. [17] described a case of a granulosa cell tumor with low FSH and LH levels. Based on animal testing, Robertson et al. suggested a partial reducing effect of inhibin B on LH during the menstrual cycle in women [16].

AMH is secreted by the granulosa cells. It is detectable once cycles begin and its level becomes insignificant at menopause. In their adult form, granulosa cell tumors can secrete this peptide [18], which was proposed as another, less probing diagnostic marker. Furthermore, the AMH level appears to be related to the mass of the tumor, as described by Chang et al. [19] and as suggested by our case.

In addition, anti-AMH immunohistochemical stainings may aid in the positive diagnosis of granulosa cell tumors in order to
differentiate them, in difficult cases, from Sertoli cell tumors or gonadoblastomas [18].

Serum markers are also useful in the changing development of these tumors and the early diagnosis of recurrence, when this relates to estradiol, inhibins and AMH. A recent article [20] was unable to demonstrate superiority between AMH and inhibins as tumor markers for granulosa cell tumors.

Our report is also of interest by showing the full imaging picture, with ultrasound and MRI, demonstrating the multiple cystic cavities associated with a tissue component, which is the aspect most frequently found [21].

4. Conclusion

A specific hormone pattern, combining a very low FSH level with a normal LH level in a patient seeking care for secondary amenorrhea requires careful etiological testing to search for a specific FSH inhibiting factor, and more specifically, inhibin B.

In our clinical case, the diagnosis of a granulosa cell tumor was made on the basis of inhibin B and AMH hypersecretion associated with an ovarian mass. AMH was also recently proposed as another marker.

These two peptides are useful for diagnosis, follow-up and monitoring for recurrences of this specific type of ovarian tumor.

Conflict of interest

No conflict of interest.

References


