APMB - Atti della Accademia Peloritana dei Pericolanti
Classe di Scienze Medico Biologiche
Vol. 105(1) 2017

ISSN 1828-6550

DOI: 10.6092 / 1828-6550 / APMB.105.1.2017.A1

Clinical Case Seminar

A1 (1-4)

Ovarian hyperthecosis coexisting with an incidental adrenal lesion: challenges in the diagnostic approach

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Abstract

Ovarian hyperthecosis is the most common cause of hyperandrogenism in women during postmenopausal age. However, its diagnosis is frequently challenging, since several causes must be ruled out, involving both adrenal glands and ovaries. Herein we describe the case of a 62 years old woman addressed to our Unit after the casual detection of an adrenal mass, compatible with an adenoma. Biochemical evaluation revealed gonadotropins in menopausal range, high testosterone and androstenedione, while the patient had been complaining of androgenetic alopecia and hirsutism for some years. Ultrasound imaging revealed only a small increase in ovarian volume, in relationship to the patient's age. A GnRHa test was performed, demonstrating gonadotropins suppression and testosterone normalization, thus confirming the suspect of ovarian hyperthecosis. The administration of these agonists, together with the slow progression of symptoms over years, play a fundamental role into excluding an androgen-secreting neoplasia, also limiting the use of ovarian veins catheterization as second line test. Besides, they represent a valid therapeutical option, especially when surgery is contraindicated (or cannot be performed).

Key-Words: Hyperandrogenism; Hirsutism; Postmenopausal Age

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Introduction

Menopausal transition is physiologically characterized by mild signs of hyperandrogenism. The reduction in oestrogen secretion generates a hormonal imbalance in favour of androgens, whose production is also supported by the high levels of gonadotropins. However, the presence of true hirsutism (i.e. hair excess in androgen-dependent areas), androgenetic alopecia, acne or virilisation can be the first manifestation of several pathological conditions. Ovarian hyperthecosis (OH) is the most common cause of hyperandrogenism in women after menopause. It consists of variable stromal hyperplasia, with high levels of gonadotropins related to postmenopausal state despite high androgen levels (1).

The diagnosis is often challenging, especially with significant confounding factors (i.e. an

ISSN 1828-6550
DOI: 10.6092 / 1828-6550 / APMB.105.1.2017.A1

incidentally discovered adrenal mass, as in our case); moreover, the exclusion of more severe diseases, like androgen-secreting tumours deriving from both adrenal glands or ovaries, is mandatory.

Clinical examination and history play a fundamental role in the diagnostic approach (2). GnRH agonists (GnRHa) represent a useful confirmatory tool, that can allow physicians to avoid more invasive procedures, like ovarian and adrenal veins catheterization (3). Their capacity of suppressing gonadotropins secretion through the down-regulation of releasing hormone receptors could constitute a valid therapeutical option, limiting the need for surgery especially when it cannot be performed for other health problems (4).

Case Report

A 62 years-old woman was referred to our Division in August 2016 because of an adrenal mass, incidentally discovered a few days before, during diagnostic evaluation for diffuse abdominal pain at the Emergency Unit. A basal abdomen CT had revealed a 1.2 cm, low density (8 HU) lesion in the right adrenal gland, primarily compatible with an adenoma. The patient was in menopause from the age of 50, and suffered from type 2 diabetes mellitus (bad blood glucose profile under insulin treatment with lispro, 22 IU at main meals and degludec, 22 IU at bedtime; HbA1c 8.9% in July 2016) and hypertension with cardiomyopathy. She was overweight (BMI 27.5 kg/m2) with a BP of 120/85 mmHg under treatment; the rest of clinical examination was unremarkable, except for moderate terminal hair (especially face and upper back) and temporal alopecia of which the woman complained since the last two years. In order to exclude adrenal hypersecretion, specific biochemical evaluation was performed: sodium, potassium and basal hormonal profile (cortisol, renin, aldosterone, 17OH-progesterone, dehydroepiandrosterone sulfate - DHEAS, urinary metanephrines and cortisol) were normal; a regular suppression of the axis after 1 mg overnight DST-test was recorded. Only total testosterone levels were frankly elevated (145.3 ng/dl; normal values range 5-75), as well as delta4-androstenedione (D4A, 4.6 ng/ml; range 0-2.83). In the hypothesis of an androgen-secreting neoplasia, further blood tests revealed negative tumour markers, while gonadotropin levels were in the postmenopausal range (FSH 58.10 mIU/ml and LH 21.42 mIU/ml). Pelvic ultrasonography showed visible ovaries without significant cysts or masses, but enlarged in relationship to patient's age (11 ml right and 12 left). A GnRHa test was performed (leuprorelin 3.75 mg im), and testosterone levels dropped to 42 and 19 ng/ml 2 and 4 weeks after administration, respectively, orienting towards a diagnosis of OH. Considering the actual comorbidities, that could be a relative contraindication to surgery, the patient will soon be started with GnRHa treatment.

ISSN 1828-6550
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Discussion

The peculiarity of this case is the coexistence of two clinical clues in the same patient: first, she was addressed to our attention for the characterization of an incidental adrenal lesion; second, the routine biochemical workup assessing a possible hypersecretion revealed hyperandrogenism of ovarian origin

(elevated total testosterone and androstenedione). Such a finding requires excluding several pathological conditions, and in this context an accurate clinical history and examination are fundamental. In fact, if some functional causes like PCOS or congenital adrenal hyperplasia from 21-idroxilase deficit are usually present before menopause, androgen-secreting tumours generally produce a rapid-onset, severe hyperandrogenism with virilisation. Our patient complained of mild hirsutism noticed over some years. On the contrary, OH is a known cause of hyperandrogenism in postmenopausal women. Its pathogenesis is still unclear, but metabolic syndrome and insulin-resistance could play a role as in PCOS (our patient was overweight with poorly controlled diabetes and hypertension, 5). Several studies have also suggested a role of hyperandrogenism in the development of metabolic syndrome, although the question is still controversial: in fact, recent evidences seem to exclude an increased cardiovascular morbidity and mortality in these patients after menopause (6). OH should always be suspected with elevated total testosterone levels and inappropriately high gonadotropins, in the absence of ovarian masses. Ovaries are usually normal on ultrasonography but, although there are no typical imaging features of these condition, a moderate increase in their volume without focal vascularization on colour Doppler has been reported in some series (5, 7). It has been related to the stromal hyperplasia due to luteinized theca cells, diffuse or in nodular clusters, as observed on histological analysis after oophorectomy (7). As stated in a recent review by Markopoulos et al, there are still no clear cut-offs in the biochemical evaluation of post-menopausal hyperandrogenism, so diagnosis relies for its most part on a thorough clinical examination and history, guiding laboratory and imaging studies (8). Several confounding factors must be considered, like concomitant adrenal masses (as observed in our case) which could make difficult to identify a pathological androgen source of ovarian origin. It has been suggested that total testosterone levels above 100 ng/dl, and particularly 140 ng/dl, should orient towards an androgen secreting tumour or OH (8). A useful diagnostic tool is based on the suppression of gonadal axis by a GnRHa, whose action leads to central receptor down-regulation. Its administration in OH results in the suppression of gonadotropin levels and the normalization of testosterone and androstenedione, demonstrating the non-autonomous hormonal secretion exerted by theca cells (3).

ISSN 1828-6550

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The same criteria support the therapeutical role of GnRHa, as it has also been reported in a series by Vollaard et al, in which three patients under treatment with depot im leuprorelin 3.75 mg every four weeks experienced the normalization of testosterone levels. It usually occurs within six months, but is already observed after one month; one patient however, who was also obese and suffered from hyperinsulinemia, had her levels decreased after 10 months, concomitantly with a significant weight reduction and improvement of insulin-resistance, thus confirming a possible role of metabolism alterations in OH pathogenesis (4).

Although enough data are lacking about long-term GnRHa treatment, it should be continued for at least 12 months for obtaining a lasting improvement in hirsutism and in biochemical profile, and theoretically it should be restarted if necessary for maintaining hormonal control (4).

Conflicts of Interest: There is no potential conflict of interest, and the authors have nothing to disclose. This work was not supported by any grant.

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Communicated and received April 6, 2017; revised May 16, 2017; published on line June 30, 2017.