Endocrine (2012) 41:342–343
DOI 10.1007/s12020-011-9566-y

LETTER TO THE EDITOR

GnRH analogue use in postmenopausal hyperandrogenism: long-term remission

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Published online: 29 November 2011

To the Editor,

The medical therapy of postmenopausal hyperandrogenism remains poorly described. The effectiveness of short-term GnRH analogues in suppressing androgens is generally indicative of the ovarian origin of the androgen production, and its benign nature [1–3], although very rarely adrenal tumours secreting androgen responsive to GnRH agonist have been reported [4]. Here we report a rare case of long-term GnRH analogue-induced suppression of androgens of ovarian origin.

A 78-year-old woman was referred for investigation of severe hyperandrogenism. She had noticed the progressive appearance of hirsuties over her face and body over a period of 3–4 years, her face becoming plethoric, with concomitant deepening of her voice which became more husky, and increasing temporal recession. She had gained around 10 kg in weight, and reported increased libido for 2 years. She was treated for hypertension with agents not considered to be causative of hirsutism. Clinical examination confirmed significant hirsutism: both her serum testosterone and androstenedione levels were markedly elevated at 21.3 nmol/l (NR < 2.9) and 17.8 nmol/l (normal 3–8), respectively, with a normal serum DHEAS. Serum testosterone failed to suppress on a low-dose dexamethasone suppression test (16.8 nmol/l at 48 h, with normal suppression of cortisol). Her serum gonadotrophins were appropriately elevated for the menopause (FSH 40.2 U/l, NR > 25; LH 21.9 U/l, NR > 16), and her estradiol appropriately low (157 pmol/L, NR 18.4–201). Basal 17-hydroxyprogesterone was normal, excluding the common form of congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Imaging (CT scanning, MRI) did not show any adrenal or ovarian abnormality, while a transvaginal US scan showed a slightly bulky uterus without thickening of the endometrium. The most likely diagnosis at this stage was either bilateral ovarian hilar cell hyperplasia or hyperthecosis, or a small Leydig cell tumour in one or both ovaries. Ovarian venous catheterisation was not considered as we have previously noticed the lack of utility of this procedure in this situation [5]. A single long-acting 10.8 mg subcutaneous injection of goserelin (Zoladex® LA, AstraZeneca) was given which induced the suppression of the serum testosterone level to 0.7 nmol/l 2 months later. The GnRH dependence of androgen secretion was taken to be indicative of an ovarian origin. Treatment with the GnRH agonist was continued for 17 months (subcutaneous injections every 3 months), and her serum testosterone levels remained within the normal range (0.9 and 1.6 nmol/l) for a further 27 months off treatment. Significant improvement of her symptoms was noticed; 11 months later the patient died from overwhelming sepsis due to methicillin-resistant *S. aureus* unrelated to her endocrine condition.

In this case, in addition to representing a functional diagnostic tool, the use of GnRH analogues offers a valuable therapeutic approach which is a particularly useful mode of therapy in patients for whom surgical intervention is not appropriate for diverse reasons. Indeed, only rare

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reports [1, 2] and our own case illustrate that long-term GnRH agonist therapy constitutes an acceptable form of treatment for post-menopausal ovarian hyperandrogenism, after exclusion of an obvious malignancy, with successful long-term suppression of serum testosterone levels. We also note that long-term suppression of testosterone may be maintained after withdrawal of therapy.

Some androgen-secreting ovarian tumours causing post-menopausal virilization are reported to be gonadotropin-responsive as opposed to being autonomous (gonadotropin-independent). The gonadotropin dependence of these tumours suggests that, as is the case for ovarian hyperthecosis, they may be developing under the stimulatory effect of high levels of gonadotropins, classically present in post-menopause. The expression of functional LH receptors on the cell surface of these ovarian tumours, in the absence of dedifferentiation, would explain their gonadotropin dependence. Both conditions can thus be controlled by GnRH agonist therapy thus avoiding surgery, but re-scanning at intervals may be advisable in the light of this possibility.

Conflict of interest The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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