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CASE REPORT - TUMOR - MENINGIOMA

Combined hormonal influence of cyproterone acetate and nomegestrol acetate on meningioma: a case report

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Abstract

Cyproterone acetate (CPA) is an antiandrogenic drug which has recently been recognized to promote the occurrence and growth of intracranial meningiomas. Nomegestrol acetate (NOMAC) is a widely used progestin-like drug that could be suggested as an alternative for patients taking CPA. We report a case of CPA-related meningioma for which relay from CPA to NOMAC led to further tumor growth and cessation of NOMAC-induced tumor shrinkage. We suggest NOMAC can have a similar effect than CPA on meningiomas. The use of NOMAC as replacement for CPA in the presence of a meningioma should be discouraged until further evidence becomes available on the role of NOMAC in such instances.

Keywords Cyproterone acetate · Nomegestrol acetate · Meningioma · Hormone therapy

Introduction

The relationship between sex hormones and meningioma occurrence or growth has been shown by various clinical and in vitro studies [1, 2]. Cyproterone acetate (CPA) is a progestin-like drug with a strong antiandrogenic effect that is currently emerging as one of the first drug able to clearly induce meningioma growth clinically [3]. Cessation of CPA can lead in many cases to tumor regression.

With the growing concern linking CPA and meningioma, there is a trend to discontinue treatment for women taking the drug. In this context, new therapeutic avenues are needed to alleviate the symptoms in patients for which CPA was initially prescribed. Nomegestrol acetate (NOMAC) is a widely used progestin agonist with moderate antiandrogenic effect that has the potential to be used as a substitute for CPA [4, 5]. We report a case of CPA-related meningioma in which cessation of the drug led to the expected tumor regression but in which relay with NOMAC led to new tumor progression. The implications of meningioma growth with NOMAC are discussed.

Case report

A 46-year-old woman with no relevant past medical history was addressed to our department following the incidental discovery of a posterior parasagittal meningioma. History revealed CPA use for the last 15 years (5 mg/day) for oral contraception since she presented painful menstrual periods with regular contraception. The patient was otherwise asymptomatic, and the neurological exam revealed no anomaly. Magnetic resonance imaging (MRI) showed a single sagittal meningioma centered on the superior sagittal sinus at the level of the parietal lobe (Fig. 1). There was no associated edema or significant mass effect. Tumor volume was measured at 11.3 cm^3.

Based on the experience of our group with CPA-related meningiomas [3], a conservative approach was favored with the discontinuation of CPA coupled with close clinical and radiological follow-up. At the same time, CPA was stopped; NOMAC was started as a replacement for her birth control medication (5 mg/day). Six months later, the meningioma started showing signs of response to the cessation of CPA with a slight regression in size on MRI (10.3 cm^3). Surprisingly, 1 year after relay from CPA to NOMAC, tumor volume increased to 15.5 cm^3. The patient remained asymptomatic. In

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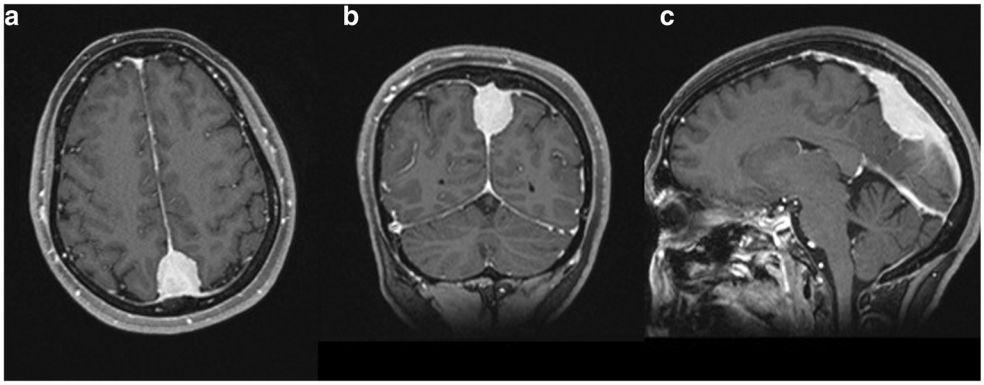

Fig. 1 Initial magnetic resonance imaging of the case. T1-weighted sequences enhanced with gadolinium showing a tumor consistent with a meningioma centered of the posterior sagittal sinus at the level of the parietal lobes. **a** Axial view. **b** Coronal view. **c** Sagittal view

view of the similarities between CPA and NOMAC, a role of the latter in tumor progression was suggested and NOMAC was also discontinued. Ten months later, the meningioma showed a significant reduction in volume (12.2 cm^3), strongly suggesting responsiveness to NOMAC (Fig. 2). The patient remained symptom-free during the whole observation period.

Discussion

Meningiomas are known to harbor progesterone receptors (PR) in 68% of cases, while a smaller number have receptors for estrogen and androgen [6]. Progesterone receptor responsiveness to sex hormones has been hypothesized to take part in the development and growth on meningiomas in multiple instances in which sex hormones are elevated such as the increased occurrence of meningiomas in females [7], congenital adrenal hyperplasia (with elevated 17-hydroxyprogesterone that can stimulate PR) [7–9], hormone replacement therapy [10], obesity [11, 12], pregnancy, and oral contraceptives. Some in vitro studies have also shown growth of meningioma cells in the presence of progesterone [13].

CPA is a synthetic antiandrogenic drug developed in the 1960s. It is currently available worldwide except in the USA. It exerts its effect via 3 mechanisms [14, 15]: competitive inhibition of testosterone-binding sites, blockade of testosterone production in the gonads, and progestin-like activity. It is currently used in the treatment of various androgen-dependent conditions such as palliative treatment of advanced prostate cancer, acne, hirsutism, alopecia, and paraphilias (off-label) and can be part of feminizing hormone therapy for transgender women [3].

Following the initial description of CPA-related meningiomas by Froelich et al. in 2008 [16], the relationship between CPA and the development of meningiomas has been investigated by other groups. Bernat et al. described to date the biggest series (12 patients) in which a decrease in size following CPA cessation was observed for all but 1 patient, in which the meningioma stabilized [3]. Gil et al. described the incidence of meningiomas among users of CPA (relative risk 11.4 with high dose) and reported a higher risk among high-dose users using it for more than a year [1]. The most common characteristics of CPA-related meningiomas from published series are as follows: female sex, multiple meningiomas, long-term use of CPA, high rate of progesterone receptors (in the few cases with available specimen), location in the anterior skull base, and tumor shrinkage after CPA discontinuation.

NOMAC is a widely used progesterone agonist mainly prescribed (alone or in combination) for contraception and treatment of menopausal symptoms [17]. It shares some similarities with CPA in regard of its mechanism of action: it possesses a strong progestin-like effect while having a moderate antiandrogenic one [18]. NOMAC holds the potential to replace CPA, for which the prescription rate is expected to drop since the release of studies linking it to meningiomas. We report the first case of meningioma progression after the relay from CPA to NOMAC. In that case, NOMAC seemingly harbored the same effect than CPA, i.e., promoting meningioma growth. Interestingly, NOMAC discontinuation also led to tumor shrinkage. Keeping in mind the mechanism of action of these two drugs, we suggest the following hypothesis for their role in meningioma growth promotion: not only the progestin-like effect could responsible for promoting meningioma growth but the antiandrogenic effect might also play a role. Via the antiandrogenic effect, a feedback loop to the hypothalamic-pituitary axis could lead to elevated levels of LHRH (GnRH), which has also been linked to meningioma growth both clinically and in vitro [19, 20]. Thus, the combined effect of progesterone agonist and LHRH could lead to significant meningioma growth.

To date, no evidence establishes a specific link between meningioma growth or occurrence and NOMAC. Interestingly, Cottin et al. reported on the diagnosis of a large meningioma in a patient taking NOMAC for 16 years for lymphangioleiomyomatosis and suggest that either this pathology or its hormonal treatment could be in involved in the

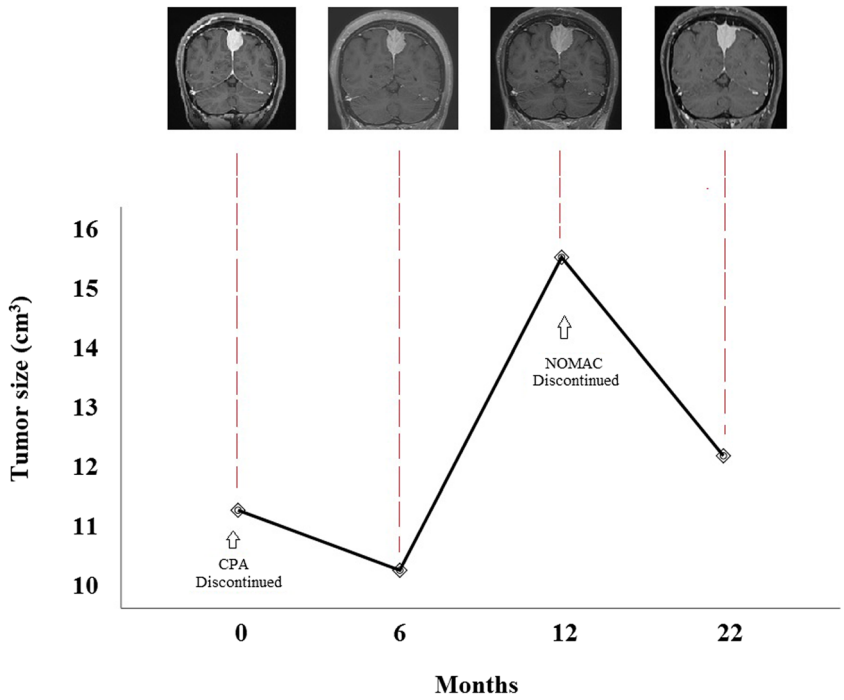

Fig. 2 Timeline of the size variation of the tumor with changes in the medication regime. Corresponding magnetic resonance imaging (T1-weighted, gadolinium enhanced in coronal view) for each follow-up time. CPA cyproterone acetate, NOMAC nomegestrol acetate

development of the tumor [21]. In that case, the meningioma was resected, preventing to assess the potential effect of drug withdrawal. If NOMAC alone could harbor to some extent, the same effect than CPA on meningiomas remains to be proven. However, this case raises awareness regarding other progestin drugs, specially those with an antiandrogenic activity. Interestingly, out of the two other progestin drugs with such activity (chlormadinone acetate and dienogest) [22], one case of meningioma regression has been reported with the discontinuation of chlormadinone acetate [23].

Conclusion

This case report demonstrates that CPA-related meningiomas can also react in the same fashion to NOMAC. In this context, the role of NOMAC as a replacement therapy for CPA when a meningioma is present should be questioned until further evidence is brought to clarify the potential mechanisms and role of NOMAC in meningioma growth.

Compliance with ethical standards

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

Patient consent The patient has consented to the submission of the case report for submission to the journal.

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