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ORIGINAL ARTICLE - TUMOR - MENINGIOMA

Spontaneous regression of meningiomas after interruption of nomegestrol acetate: a series of three patients

Thibault Passeri[1] · Pierre-Olivier Champagne[1] · Anne-Laure Bernat[1] · Shunya Hanakita[1] · Henri Salle[1] · Emmanuel Mandonnet[1] · Sébastien Froelich[1]

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Abstract

Background The relationship between increased meningioma incidence and growth and long-term hormonal therapy with cyproterone acetate (CPA) in women has been recently established in literature. Following the raise in awareness from hormonal treatment, we describe a potential relationship between the progesterone agonist nomegestrol acetate (NOMAC) and meningioma growth.

Methods After implementation of a screening protocol to detect potential interactions between hormonal exposure and occurrence of meningioma, we identified patients taking NOMAC and newly diagnosed with a meningioma. NOMAC was stopped and those patients were followed tightly both clinically and radiologically. Retrospective volumetric analysis of the tumors was performed on the imaging.

Results Three patients were identified for the study. After cessation of the NOMAC, tumor shrinkage was documented for all meningiomas within the first month. Up to 70% of tumor volume reduction was observed during the first year of follow-up in one of them. None of the patients developed new symptoms.

Conclusion We report the first cases of meningiomas responsiveness to discontinuation of hormonal therapy with NOMAC. Similarly to cases associated with long-term CPA intake, tumor reduction, and improvement of clinical symptoms can be observed after cessation of NOMAC.

Keywords Progestational agonist · Meningioma · Cyproterone acetate · Nomegestrol acetate

Introduction

Meningiomas are the most common cerebral tumor after metastasis [22] and are known to present a clear female predominance, with a female to male ratio of 2.3:1 [22]. Clinical as well as in vitro studies have established a correlation between sex hormonal therapy, mainly progesterone derivatives, and the occurrence of meningioma [8, 9, 21]. Although there is still controversy as to whether hormonal replacement therapy and low-dose contraceptive agents can induce the development of meningiomas, the long-term use of high doses of cyproterone acetate (CPA), an antiandrogenic drug, has been recognized in recent years to promote the development of meningiomas. In such instances, rapid clinical improvement and significant reduction of the tumor volume can be seen after CPA withdrawal [3–5, 12].

Nomegestrol acetate (NOMAC) is a highly selective progestogen derived from 19-norprogesterone [11, 27]. It is available in many countries either alone or in combination with estrogen and is mostly prescribed for oral contraception and menopausal hormonal therapy. As of now, there exist no specific safety concerns between NOMAC exposures and the development or growth of intracranial tumors. In the current study, we shed light on a new association involving NOMAC and intracranial meningiomas in a series of three patients in whom tumor shrinkage occurred following NOMAC withdrawal.

This article is part of the Topical Collection on *Tumor - Meningioma*

✉ Pierre-Olivier Champagne
pierre_olivierc@hotmail.com

[1] Department of Neurosurgery, Lariboisiere Hospital, University of Paris Diderot, 2 rue Ambroise Paré, 75010 Paris, France

Methods

Patients selection

From early 2010, following the results of CPA studies, an awareness protocol was implanted at our institution to screen for patients taking CPA and help document possible interactions between hormonal intake and meningiomas. Each patient, newly diagnosed with an intracranial tumor compatible on imagery with a meningioma, was systematically questioned about hormonal intake. We identified patients harboring one or multiple meningiomas and taking NOMAC. Based on our experience in establishing the relationship between meningiomas and CPA [3], NOMAC was stopped and the patient monitored with close clinical and radiological follow-up. To be eligible for NOMAC cessation trial, patients had to harbor a meningioma in which medium-term stability was deemed safe. Patients having received prior brain radiation and/or diagnosed with neurofibromatosis of any type were excluded. This study was approved by our institution local review board and patient's informed consent was obtained prior to involvement into the study.

Files analysis and volumetric study

Patients' medical charts were retrospectively studied for demographic data and clinical evolution. Carestream ® software was used to measure and compare tumor volume on magnetic resonance imaging (MRI). One observer performed tumor volumetric measures using Carestream® using DICOM data. The outline of the meningioma was traced manually on each slice. After selecting all of the regions of interest within one series, the volume was automatically calculated using the region of interest (ROI) segmentation function.

Results

Three patients were identified for analysis, all of which were females with a long period of NOMAC intake (mean, 25 years) (Table 1). NOMAC daily intake was 5 mg (highest dose available) for all of them. The medication was discontinued in all cases considering the possible association between the drug and the development of meningiomas. One patient stopped the medication on her own volition 1 year before diagnosis and was encouraged to remain off from it. At the moment of the study, none of them had undergone surgery for meningioma. Tumor shrinkage was observed in all of cases within a period ranging from 4.5 to 12 months.

Case 1

A 37-years-old woman came seeking medical attention following right-sided focal seizures. History revealed long-standing headaches memory loss and asthenia. She has been taking NOMAC for the last 20 years for oral contraception. MRI showed a left-sided large (54.5 cm^3) paraclinoidal meningioma spanning the left greater sphenoid wing surrounded by edema. There was an evidence of tumor necrosis in the center of the tumor. A smaller meningioma (1.8 cm^3) located on the contralateral sphenoid ridge was also detected (Fig. 1). One month after cessation of the NOMAC, MRI revealed a significant volume decrease of the left sphenoidal meningioma (40.7 cm^3) as well as peritumoral edema. There was also a significant clinical improvement of all her symptoms and no further seizure was noted. On last follow-up 1 year after cessation of NOMAC, additional tumor volume reduction was observed for both meningiomas with a volume reduction of 76% (13.1 cm^3) of the largest meningioma (Fig. 1).

Case 2

A 68-year-old woman was addressed to our department after the discovery of clival meningioma following long-standing diminution of visual acuity on the left side after unsuccessful cataract surgery. She presented no visual field defect. MRI confirmed the presence of a clival meningioma (12.4 cm^3) extending to the sella and the left optic canal, possibly contributing to the loss of visual acuity (Fig. 1). Ophthalmologic exam showed left optic atrophy. She has been taking NOMAC for 20 years for symptoms related to menopause. NOMAC cessation was favored over surgery in that case since visual symptoms were of mixed etiology and chances of recovery were deemed low with the presence of optic nerve atrophy. On last follow-up, 4 months after NOMAC cessation of the MRI showed a significant decrease of meningioma volume (10.3 cm^3, 17% volume reduction) and stability of her visual acuity (Fig. 1).

Case 3

A 54-year-old woman was referred to our department for the fortuitous discovery of two meningiomas following a minor trauma. She was otherwise asymptomatic and has been taking NOMAC for at least 35 years for contraception and stopped it a year before meningioma diagnosis. Initial MRI revealed a right frontal meningioma (5.7 cm^3) and another meningioma over the left clinoid (9.4 cm^3) (Fig. 1). There was also a left temporal meningeal thickening. On the last follow-up 7 months after discovery of meningiomas, we observed a decrease of 15% (7.9 cm^3) for the left clinoid meningioma and 9% (5.2 cm^3) for the right frontal meningioma with meningeal thickening. The patient remained asymptomatic.

Table 1 Summary of meningioma cases associated with long-term use of NOMACs

Case no.	Age (year), sex	Symptoms	Number of tumors	Tumor location	NOMAC indication	Length of medication (years)	Daily dose (mg)	Treatment	Tumor shrinkage
1	37, F	Headaches, partial epilepsy, memory loss, and asthenia	2	Left greater sphenoid wing Right sphenoid ridge	Birth control	20	5	Drug withdrawal	Yes
2	68, F	Loss of vision on the left side	1	Clivus	Menopause	20	5	Drug withdrawal	Yes
3	54, F	No symptom	2	Left clinoid Right frontal	Birth control	35	5	Drug withdrawal	Yes

Discussion

The association between sexual hormones and the incidence or growth of meningiomas is supported by many factors including a high female predominance (2.3:1), strong expression of progesterone receptors in meningiomas, tumor growth during the luteal phase of the menstrual cycle and pregnancy, spontaneous regression after pregnancy, and association of meningioma and breast cancer [6]. The level of expression of progesterone receptors is higher in meningiomas than in normal meningeal tissue and the expression of these receptors is higher in women [23]. Although the majority of

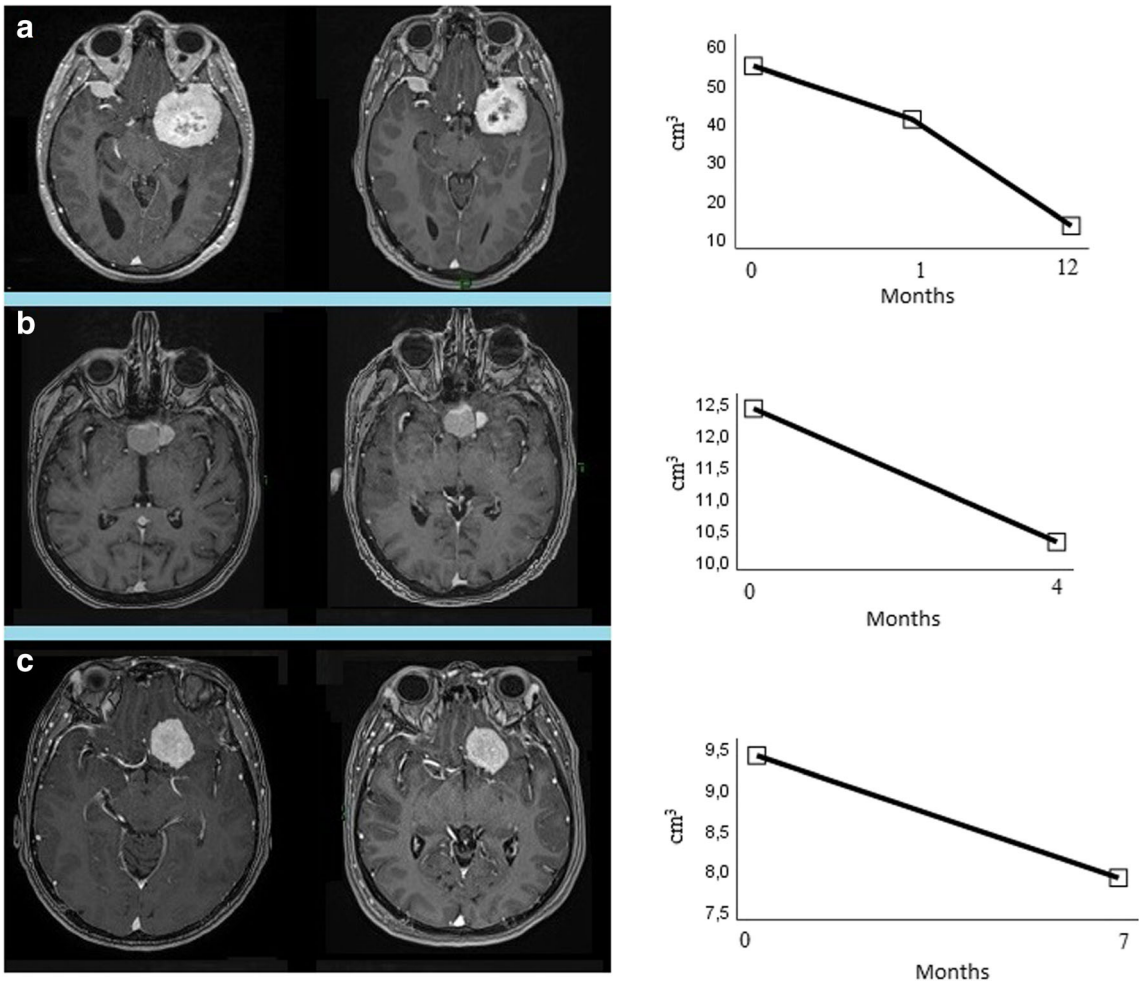

Fig. 1 Volumetric evolution of the most significant tumor in the three cases. Initial image (axial T1 with gadolinium) on the left panel, image of the last follow-up (axial T1 with gadolinium) on the right panel, and graphical representation of the tumor volume between the first and last imaging studies. **a** Case 1. **b** Case 2. **c** Case 3

meningiomas lack estrogen receptors, up to 80% of benign meningiomas express progesterone receptors. Some authors have reported elevated progesterone receptor levels to be a marker of favorable prognosis, whereas low progesterone receptor levels or isolated expression of estrogen receptors correlate with increased tumor aggressiveness and increased risk of recurrence [24, 25]. Pregnancy also appears to accelerate growth and some cases of tumor resorption after delivery have been described [13, 14, 18]. This is in accordance with a hormonal sensitivity of these tumors, with the increase of various sex hormones during pregnancy promoting growth and their falling level after delivery leading to regression.

NOMAC is one of the most widely used progesterone agonists. Indications for NOMAC include the treatment of some gynecological disorders (fibromas, menstrual disorders etc.), contraception, and treatment of menopausal symptoms [16]. We report a series of three cases in which cessation of NOMAC after its long-term use was related to tumor shrinkage, preventing the need for surgery. We believe the observed shrinkage to be directly related to the cessation of NOMAC and not to be fortuitous. Two factors support that claim. First, spontaneous meningioma regression without hemorrhage or external interference is an exceptional event [10, 28]. Secondly, NOMAC shares some similitudes with CPA, which is associated with an increased incidence of meningiomas after long-term use with high dosage [3]. Moreover, a significant reduction of the tumor's volume was observed in many cases after cessation of CPA [4, 5, 12]. NOMAC is a strong progesterone agonist while having a moderate antiandrogenic activity and strong antiestrogenic activity [20]. On the other hand, CPA is a strong antiandrogenic with moderate progesterone activity. These similitudes in the hormonal potency between NOMAC and CPA could help explain the observed effect in the current study. Another similarity lies in the meningiomas themselves. CPA-related meningiomas are more prone to be localized in the anterior skull base and convexity and tend to be multiple. In the current series, two out of three cases harbored multiple meningiomas and all of them were in the anterior skull base.

The exact mechanisms by which NOMAC and CPA could promote meningioma growth are still unclear, but in view of the similitudes between the two, we advance a hypothesis regarding their potential mechanism of action in that regard. On top of the well-recognized effect they could bear on progesterone receptors on meningiomas, these drugs could also promote meningioma growth via augmented secretion of the gonadotropin-releasing hormone (GnRH, or LHRH). GnRH analogues used for prostate cancer have been reported to induce meningioma formation [1, 15, 26]. This could be mediated via GnRH receptors, present in up to 88% of meningiomas [17]. The growth-promoting action of GnRH on meningioma cells have also been observed in vitro [7]. Progestogens such as NOMAC and CPA have the potential to lead to augmented secretion of GnRH by the hypothalamus. Three sex steroids have a negative feedback on GnRH secretion at the level of the hypothalamus: estrogen, progesterone, and testosterone [19]. Via their antiandrogenic and antiestrogenic effect, NOMAC and CPA could diminish the negative feedback on the hypothalamus, thus augmenting secretion of GnRH. Nevertheless, the net effect of CPA and NOMAC on brain levels of GnRH remains unknown and more studies are needed to define its potential role in CPA and NOMAC-related meningiomas.

The time and quantity of exposure to NOMAC also seems to play a major role, since all reported cases in the current study have received the highest available dose for at least 20 years. Another interesting aspect in meningioma response to NOMAC lies in the rapidity by which meningioma regression occurred after cessation, with measurable shrinkage that can be seen as soon as 4 months after it.

In the first case, after interruption of NOMAC, the left sphenoidal tumor rapidly decreased during the first 6 months (Fig. 1). Then, the size continued to decrease but less rapidly. This caveat is an important consideration in some particularly large lesions with significant mass effect or severe clinical symptoms. Like in some CPA-related cases, an initial conservative approach with NOMAC withdrawal and close follow-up could be tried even in voluminous meningiomas with severe symptoms [2]. In such cases, careful follow-up should be instigated since tumor shrinkage is not always assured. Stemming from our experience with CPA-related meningiomas, we believe there could be two types of tumors: those already present at the time of the beginning of hormonal treatment and those arising from such treatment. In the former, tumor growth is expected to halt or diminish but regression is less likely. In the latter group, meningiomas tend to be multiple and regress with the cessation of hormonal treatment [3–5]. These meningiomas could also yield a specific genetic profile [12].

Although a strong interaction between CPA and intracranial meningiomas has been recognized, a similar relationship with another drug such as NOMAC must be confirmed by further observations before refinement of the indications for such medication can be advised. This is especially true given the high prescription rate of NOMAC. To our knowledge, this is the first report of such meningioma volume shrinkage after discontinuation of NOMAC.

Conclusion

Similarly to CPA, NOMAC may interact with intracranial meningiomas. We report three cases of tumor regression after cessation of hormonal therapy with NOMAC. Close clinical and radiological follow-up is highly recommended after medication discontinuation. This series opens new insights into the role of progesterone agonists with antiandrogenic effect in meningioma tumorigenesis.

Compliance with ethical standards

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

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (name of institute/committee) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Patient consent Informed consent was obtained from all individual participants included in the study.

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