Atypical Evolution of Meningiomas After Discontinuation of Cyproterone Acetate: Clinical Cases and Histomolecular Characterization.

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Abstract

Purpose

Long-term use of cyproterone acetate (CPA) is associated with an increased risk of developing an intracranial meningioma. Discontinuation of CPA most often induce stabilization or regression of the tumor. The exact mechanism of regression is unknown as well as the reason why some meningiomas are still growing after CPA discontinuation. We are reporting four patients with multiple meningiomas, showing opposite tumor evolutions after stopping the CPA highlighting the underlying histologic and genetic features.

Methods

Patients presenting several meningiomas with opposite evolutions following the discontinuation of CPA were identified. The clinical and radiological data's were reviewed. A retrospective volumetric analysis of the meningiomas was performed. All the growing meningiomas were operated. Each tumor was characterized histopathologically and by molecular and genetic analyses.

Results

Four female with multiple meningiomas and opposite tumor volume evolution after CPA discontinuation were identified. The histopathological results found fibroblastic meningiomas for tumors growing located in the convexity and a more fibrous meningioma in the skull-base tumor which decreased. Meningothelial and transitional meningiomas were found in two skull-base growing meningiomas. The molecular characterization found two *NF2*-mutations among the 4 growing meningiomas. In one patient who presented both patterns, the shrinking skull-base tumor harbored a *PIK3CA*-mutation whereas the growing tumor, a *NF2*-mutation.

Conclusion

To our knowledge, this is the first report of such an atypical tumor evolution of CPA-associated meningiomatosis after CPA discontinuation in the same patient. Underlying biological mechanisms explaining this observation especially, the close relationship between mutational landscapes and the meningeal embryology in CPA-related meningiomas require further research.

Introduction

The association between sex hormones and meningiomas is well known with arguments such as an incidence more than 2.5 times higher in women[1], tumor growth during pregnancy and regression following child birth[2], association between meningiomas and breast cancer[3], endometrial carcinoma, endometriosis[4] and, expression of progesterone receptors (PR) and oestrogene receptors (ER) in meningiomas[5].

Cyproterone acetate (CPA) is a synthetic progestin drug with strong antiandrogenic effect used for a variety of indications, mostly related to hyperandrogenization and hirsutism in women, while it is used for prostate cancer and paraphilia in men. The suspicion of a relationship between the use of CPA and the risk of intracranial meningiomas and, the regression after CPA discontinuation was first reported in 2008 by Froelich et al.[6] and was followed by numerous case reports or series[7–18]. This increased risk and a strong dose-effect were recently proven in a large epidemiological study in France[19]. For progestin-related meningiomas and particularly in the case of CPA, our experience and those of others showed that, when the treatment is discontinued, most of the tumors stabilize in size or decrease, avoiding the need for further surgery[7, 8, 11, 12, 15, 16, 20]. Thus, most authors now recommend careful follow-up instead of active treatment if urgent surgery is not needed. However, the long-term behaviors of regressive progestin-related meningiomas are still unknown.

Concerning the molecular standpoint, recent reports have shown that pathogenic *PIK3CA/AKT1* mutations are more frequently found in progestin-associated meningiomas[21, 22]. Meningioma mutations affecting the *PIK3CA/AKT1* pathway are also more frequent in skull base location whereas meningiomas arising from the convexity or the posterior fossa harbor mutations in the *NF2*-gene[21, 23–25]. Distinct embryologic origins of the meninges[26] may explain some variation in the mutational landscapes of meningiomas.

We are reporting a series of CPA induced meningiomatosis with opposed tumor evolution following CPA discontinuation in the same patient, highlighting the underlying histologic and genetic features.

Material And Methods

Patients' selection

Since 2009, following the results of our CPA studies[7, 8, 12, 13, 20, 27], every patient presenting with a meningioma to our neurosurgical department was questioned about previous history of progestin treatment. Every newly diagnosed patient with intracranial tumor radiologically compatible with a meningioma associated with CPA intake, followed a conservative strategy starting with discontinuation of CPA and a close clinical and radiological follow-up. Surgery was only indicated in case of tumor growth on serial magnetic resonance imaging (MRI) or in severely symptomatic patients.

All patients with meningiomatosis (>1 meningioma), CPA exposure(>3g for six months) and opposed patterns of tumor evolution after CPA discontinuation were included. Patients presenting prior radiation and/or meeting the clinical criteria for the diagnosis of familial schwannomatosis or type 2 neurofibromatosis were excluded. For each patient, clinical and radiological tumor characteristics, CPA history and follow-up were collected.

Files analysis and volumetric study

Patients' charts were retrospectively studied for demographic data and clinical evolution. Carestream® software (Carestream Health Inc, Rochester NY, USA) was used to measure and compare tumor volumes on MRI. The outlining was performed by two board certified neurosurgeons by manually contouring each meningioma on each slice on the axial reconstructions of the 3D T1 gadolinium enhanced MRI sequences, and subsequently verified in the sagittal and coronal planes. The contouring was then optimized with the "repulsor" tool. The volume was automatically calculated using the region of interest segmentation function.

Histopathologic review

The histological analysis was performed by two neuropathologists (H.A-B and M.P). Tumors were classified according to the 2016 WHO grading[28]. Histopathological parameters were evaluated and immunohistochemistry studies (ABC peroxidase, DAB automate, Venta Benchmark) including antibodies directed against Ki-67 and progesterone receptors were performed for each available sample.

Biomolecular characterization (Targeted Next Generation Sequencing)

Each available tumor was analyzed for protein-coding gene mutations by targeted next-generation sequencing (NGS). The in-house NGS panel included 571 genes of interest in oncology for diagnosis, prognosis, and theranostics including meningioma genes of interest such as *NF2*, *PIK3CA*, *AKT1*, *SMO*. The library preparation was performed using the Agilent Sureselect XT HS kit according to the manufacturer protocol, and the sequencing was completed on an Illumina NovaSeq 6000 sequencer. All variants, named using Varscan2 (v2.4.3-0), that passed the following thresholds were validated: allelic ratio above 5% and population frequency lower than 0.1% in 1000 g, ESP or gnomAD. This large targeted NGS panel also allowed molecular analysis of tumors for copy number variation (CNV).

Ethics statement

All patients provided written consent for future publications for academic purposes and for translational researches. The study was approved by the local ethics committees.

Results

Between April 2009 and August 2019, 132 patients with CPA-related meningiomas were included in our prospective database. The mean follow-up time was 38 ± 29 months (median, 18 months). After applying inclusion and exclusion criteria, four patients with opposed patterns of meningioma growth after CPA cessation were identified. Patients had been taking CPA for a long period from 5 to 26 years (mean: 15.8 ± 9.9 years). The doses of CPA ranged from 25 to 50 mg daily. In all of these four patients, one meningioma was surgically removed because of tumor growth, while others were clinically followed because decreasing in size (Fig 1). In one patient (case2), the growing and decreasing tumors were next to each other and were resected together. The targeted NGS panel with CNV status was performed for the

four growing meningiomas and for one decreasing meningioma (case 2). Patients and tumor characteristics were summarized in Table 1.

Clinical, histological and molecular results

Case 1

A 45-year-old female who had been taking CPA for five years for dysmenorrhea and alopecia was referred to our department following the MRI diagnosis of two asymptomatic meningiomas (right occipital attached to the tentorium and right frontal). Both presented a homogeneous gadolinium-enhancing MRI signal.

CPA was stopped at the time of diagnosis. Over a period of 2 years of observation, the tentorial occipital tumor continued to grow (5.3 to 6.1 cm³), while the smaller frontal meningioma shrank (0.08 to 0.03 cm³). The occipital lesion was operated. Anatomopathological examination found a fibroblastic meningioma with a Ki-67% <1% and a level of PR >75%. *ANF2* pathogenic variant (c.399C>A / p.(Cys133Ter)) was identified in this meningioma (Fig 1).

Case 2

A 62-year-old female who had been taking CPA for 22 years for alopecia presented with two lesions: a millimetric right frontal meningioma and a large, asymptomatic left temporal fossa meningioma of 35 cm³. The last one was composed of two parts with distinct MRI signals after gadolinium injection: a temporal convexity part with homogeneous gadolinium-enhancement and a more medial spheno-orbital part with heterogeneous gadolinium enhancement.

The CPA was stopped, and several control MRIs were done for 11 months, showing a progression of the convexity part of the large meningioma (3.9 to 7.6 cm³), although the spheno-orbital part of the tumor decreased in volume (31.1 to 16.6 cm³). The other frontal meningioma completely disappeared. Given the radiological progression, a surgical treatment for the temporal fossa meningioma was considered appropriate. The histopathological examination was consistent with a fibroblastic meningioma for both parts of the tumor, but a more fibrous feature for the skull-base part. The proliferation index (Ki-67) was elevated in the convexity part, superior to 12 %, while <1% in the spheno-orbital part (Fig 2). The progesterone-receptor status was positive for the two components but inferior to 30 % in the growing part. Concerning the molecular standpoint, we observed a *NF2* pathogenic variant (c.241-1G>A) in the convexity growing part. Loss of chromosomes 22 and X was also identified in CNV analysis. In the spheno-orbital part of the tumor that regressed in size, a *PIK3CA* pathogenic variant (c.1633G>A / p.(Glu545Lys)) was observed. Each component of the tumor did not harbor the mutation found in the other part. Moreover, CNV analysis confirmed the two different tumoral entities (Fig 3).

Case 3

A 53-year-old female was referred to our department complaining of progressive memory loss. She had been taking CPA for more than 10 years for acne. An MRI identified two small meningiomas, one olfactory groove meningioma (0.7 cm³) and one in the left parietal region (1.1 cm³) and alopecia. Both presented a homogeneous gadolinium-enhancing MRI signal. It was therefore decided to stop CPA. During a follow-up period of 41 months, a consistent volume increase of the olfactory meningioma (0.7 to 5.2 cm³) was observed together with the regression of the left parietal tumor (1.1 to 0.4 cm³). The olfactory meningioma was successfully operated. The anatomopathological examination showed a transitional meningioma with a Ki-67 <2% and a PR level >75%. No pathogenic variant was identified.

Case 4

A 42-year-old female, treated with CPA for 26 years for alopecia and oral contraception, was referred to our center following the fortuitous discovery of several asymptomatic meningiomas (tuberculum sellae, right frontal convexity, two millimetric left frontal and one millimetric left parietal). CPA was stopped, and the patient was observed. After the 15-month follow-up, the right frontal meningioma decreased in volume (13.4 to 9.6 cm³) while the tuberculum sellae meningioma continued to grow (15.7 to 21 cm³) with a slight proximal and medial extension into the left optic canal. The other millimetric meningiomas of the convexity shrunk. The tuberculum meningioma was successfully removed, and the histopathological examination confirmed a meningothelial meningioma with a Ki-67 <4-5 % and a PR level >75%. No pathogenic variant was identified.

Discussion

The suspicion of a link between CPA and meningiomas was raised by our group in 2008[6] and was confirmed by numerous case series showing regression or stabilization of meningioma(s) after CPA discontinuation[7, 8, 12, 13, 15, 17, 18, 27, 29–32]. Gill et al.[14] described an increased risk of meningioma(s) in patients under high dose CPA and with a longer than 1 year exposure. Recently, Weill et al.[19] proved this increased risk of meningioma(s) development with long term use of CPA and a strong dose effect[19].

CPA-related meningiomas also seem to be more often multiple and localized on the anterior or mid-skull base and the anterior convexity[21, 22]. It is well known that the meninges have different embryological origins[33] depending on the anatomical site; this embryological origin might be associated with the pathophysiology of various diseases such as meningiomas[26, 34]. Recently, Okano et al[24] demonstrated that oncogenic mutations and meningioma characteristics (tumor location, histological findings) are associated with meningeal origins. Tumors from meninges originating from the neural crest more frequently harbor *NF2* mutations or 22q loss[23, 24, 35], and are associated with more frequent fibrous histological type[24]. Meningiomas with *NF2* mutations are also associated with the posterior skull base location that originates from the dorsal mesoderm. The tumors arising from the meninges originating from the paraxial mesoderm harbor preferentially *AKT1*, *SMO*, *KLF4* and *PIK3CA* mutations and are frequently associated with meningothelial meningioma type[24].

The mechanism(s) of pathogenesis of multiple sporadic meningiomas remain unclear, and two hypothesis have been raised: a monoclonal origin[36] or an independent development[36, 37] suggesting several mutational landscapes. Concerning progestin-associated meningiomas which account for almost one third of the multiple meningioma, they seem to be characterized by a specific mutational landscape. *PIK3CA* pathogenic mutations were identified in progestin-associated meningiomas in comparison with a control population[21, 22].

This is the first report of CPA related meningiomatosis with opposed evolution of meningiomas in the same patient after CPA discontinuation with regressing tumors while other meningiomas continued to growth. The most striking example of this differential growing pattern is case 2 in which two components exhibiting opposite behavior with volume increase of the convexity component along with a decrease in size of the skull base component. In our patients, *NF2*-mutations were identified in the growing tumors, although a *PIK3CA* mutation was only found in the tumor shrinking after CPA discontinuation.

Two main hypotheses could be evoked to clarify this atypical phenomenon.

The first hypothesis for the opposed profile evolution of meningiomas in a same patient after cessation of CPA is the coexistence of hormone-related and not meningiomas with specific mutational landscapes.

For case 2, the hypothesis of two different meningiomas which would later unify in a single entity is plausible considering their distinct genetic profiles (Fig 3). It would imply the coexistence of two tumoral clones (hormonal or not induced) in a same patient, characterized by a different mutational landscape and probably different underlying tumorigenesis mechanisms.

Furthermore, our results are in concordance with previous reports of an association between the mutational landscape of meningiomas and the embryological origins of the meninges from which they arise. All growing-meningiomas harboring *NF2*-mutations were localized in the convexity or the tentorium (who is originated from the neural crest) and were fibroblastic meningiomas. In the case 2, the sphenoorbital part of the meningioma, decreasing in volume after CPA-discontinuation, harbored a *PIK3CA*-mutation that is common in CPA-related meningiomas[21]. However, not only driver genetic mutations can explain the tumorigenesis of CPA-related meningiomas but also the epigenetic regulation and methylation status which is commonly implicated in tumor progression[38].

A second hypothesis that all meningiomas were hormone-related but prolonged exposure could generate loss of progesterone receptors.

PR are found in most meningiomas[5] and are believed to play a significant role in meningioma growth[39]. Progestin exposition could induce the growth of meningeal cells through their intracellular receptors in concert with coactivators and corepressors[10]. Previous reports indicated that loss of PR status has been associated with a high cellular proliferation, mitotic index (Ki-67), recurrence and high-grade tumors[40, 41]. Moreover, according to the tumor location, meningiomas express different patterns of sex hormonal receptors[42]. CPA-related meningiomas often present a higher PR expression than non-

CPA meningiomas[42], and *PIK3CA* mutations occurred also more frequently in the presence of the hormone receptor overexpression[43].

Long-term and high-level progesterone stimulation could generate tumoral genomic alterations in CPA-meningiomas leading to progressive loss of progesterin tumor receptors, thus explaining a continued growth of these tumors even after CPA withdrawal. This hypothesis refers to the mechanisms of drug resistance in patients with advanced cancers, thus selecting some clonal tumor cells. One of them includes genetic alterations leading to an abnormal conformation protein that impair the binding of the drug.

This hypothesis is also consistent with the pathological findings of our case 2 in which we observed a PR level lower than 30% and Ki-67 at 12 % in the convexity growing part of tumor harboring a *NF2*-mutation. However, in the cases 3 and 4, we observed in the skull base growing meningiomas a classic higher level of PR with a low Ki-67 rate as well as in the tentorial meningioma of the case 1.

If a genetic predisposition to CPA meningiomatosis exists, as suggested by familial cases[44], it must not be the only explanation considering the coexistence of two hormone response patterns. Other factors in the genesis of these tumors remain to be determined. As the number of patients followed for progesterin-related meningiomas increased significantly in the last years, it is important to understand why some meningiomas continue to grow meanwhile most of them regresses or stabilize.

Conclusion

In cases of CPA-related meningiomatosis, when CPA is discontinued, most of the tumors stabilize in size or even shrink. However, as shown in this report, exceptions are possible and some meningiomas even in the same patient, continue to grow emphasizing the importance of a careful and prolonged patient follow-up. Although several hypotheses can be proposed, the underlying biological mechanisms remain unclear and deserve further studies in patients harboring opposite growth patterns, in order to predict those meningiomas that will continue to grow and improve patient counselling for newly diagnosed progesterin related meningiomas.

Declarations

Conflict of interest

None of the authors declare a conflict of interest

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Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by TP, LG, RA, JW, AP, CB, MP, HAB, ALB, JMP, EM and SF. The first draft of the manuscript was written by TP and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding on reasonable request.

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Tables

Table 1 Patients and tumor characteristics were summarized.

	Case 1	Case2	Case 3	Case 4
Sex	Female	Female	Female	Female
Age at diagnosis (y)	45	62	53	42
Symptoms	None	None	Memory impairment	None
Treatment duration (y)	5	22	10	26
N° of meningiomas	2	3	2	5
Growing meningiomas				
N° of tumors	1	1	1	1
Location	Occipital tentorium	Temporal convexity	Olfactory groove	Tuberculum
WHO grade (I/II/III)	Grade I Fibroblastic	Grade I Fibroblastic	Grade I Transitional	Grade I Meningothelial
PR (low/high ¹)	High	Low	High	High
Ki-67(%) (low/high ²)	Low	High	Low	Low
Mutations	<i>NF2</i>	<i>NF2</i>	NC	NC
Meningeal embryological origin	Neural crest	Neural crest	Paraxial Mesoderm	Paraxial Mesoderm
Shrinking meningiomas				
N° of tumors	1	2	1	4
Location	Frontal convexity	Spheno-orbital / Frontal convexity	Parietal convexity	Frontal and parietal convexity
WHO grade (I/II/III)	NA	Grade I Fibrous *	NA	NA
PR (low/high ¹)	NA	High*	NA	NA
Ki-67(%) (low/high ²)	NA	Low*	NA	NA
Mutations	NA	<i>PIK3CA</i> *	NA	NA
Meningeal embryological origin	Neural crest	Paraxial Mesoderm* / Neural crest	Neural crest	Neural crest

¹ PR positivity > 75%

² Ki-67% > 10%

* Alone the spheno-orbital meningioma was analyzed

PR= progesterone receptors

Figures

Figure 1

Time of diagnosis (left image) and preoperative (right image) MRI (axial T1 or sagittal T1-weighted sequences enhanced with gadolinium) with graphical representation of the tumor volumes evolution (right panel). A) case 1; B) case 2; C) case 3; D) case 4.

Figure 2

Histological and immunohistochemical (against PR) comparison between the growing part of the tumor harboring a NF2 variant (A,B) and the PIK3CA shrinking part of the tumor (C,D). Case 2. The tumoral part harboring the PIK3CA variant was a fibrous tumor (C) in which all the tumoral cells stain PR (D) whereas the other part stain positively the PR but inferior to 30 % (B). Original magnification $\times 20$.

Figure 3

Copy number variation profile of the two tumoral patterns described in the case 2 showing two different tumoral entities. Loss of chromosomes 22 and X (red circle) was observed in the convexity component harboring a NF2 mutation (A), while the spheno-orbital part (B) harbored no loss of chromosomes 22 or X (red arrow) but a PIK3CA mutation.