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Case Report

Giant Intracranial Meningiomas Requiring Surgery in 2 Transgender Women Treated With Cyproterone Acetate

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Abstract

Progestin-associated meningioma is a rare complication of cyproterone acetate (CPA), an anti-androgen commonly prescribed in feminizing hormone therapy regimens for transgender and gender-diverse individuals. A dose-response association has been observed, particularly with longer-term exposure to doses ≥ 50 mg daily; however, the dose below which CPA use is safe remains unclear. We herein report the cases of 2 transgender women using CPA who developed meningioma. Novel aspects of our cases include: (i) the presence of symptomatic giant meningiomas (> 5 cm), including multiple meningiomas in one patient, requiring urgent surgical intervention; (ii) meningioma development with both high-dose, long duration and low-dose, shorter duration CPA; and (iii) the presence of a *PIK3CA* missense variant in one patient, which may play a role in the pathogenesis of progestin-associated meningioma. Our cases highlight the real-world risk of this likely underreported adverse effect and underscore the importance of clinician vigilance for neurological sequelae. We suggest using the lowest dose of CPA that maintains adequate androgen suppression, with consideration of alternative anti-androgens where appropriate.

Key Words: meningioma, cyproterone acetate, transgender, gender affirming hormone therapy

Abbreviations: CPA, cyproterone acetate; GAHT, gender affirming hormone therapy; MRI, magnetic resonance imaging; NGS, next-generation sequencing; WHO, World Health Organization.

Introduction

Meningiomas are the most common primary intracranial tumor in adults, with an estimated age-adjusted incidence of 8.8 per 100 000 population per year (1). They are graded by the World Health Organization (WHO) as grade 1 (non-malignant), grade 2 (atypical), and grade 3 (malignant); over 80% of meningiomas are WHO grade 1 (2). Meningiomas larger than 5 centimeters are categorized as giant, and are more likely to involve critical neurovascular structures, increase intracranial pressure, and entail more complicated surgical resection (3). Abundant expression of progesterone receptors in arachnoid tissue, from which meningiomas arise, is well established; progesterone receptor expression is documented in greater than 80% of meningiomas (4, 5). A smaller percentage of meningiomas (up to 20%) may also express estrogen receptors (6).

Cyproterone acetate (CPA) is a synthetic, progesterone-like compound that has been used in combination with estradiol in feminizing gender affirming hormone therapy (GAHT) regimens for transgender and gender-diverse (trans) individuals since the 1980s. CPA is a potent progestogen which exerts negative feedback on the hypothalamic-pituitary-gonadal axis to decrease gonadotrophin secretion and testosterone concentrations, as well as being a moderate androgen receptor antagonist (7).

CPA is the most frequently used anti-androgen in many European countries, and until 2017 was commonly prescribed in high doses (> 50 mg) (8, 9). CPA is not licensed in the United States and spironolactone is the most commonly prescribed anti-androgen.

In recent years, CPA doses have been gradually lowered due to concerns about adverse effects including depression, liver enzyme derangement, and hyperprolactinemia (10). More recently, concerns have been raised regarding the development of meningioma with long-term use, especially higher cumulative doses (5, 9). CPA use in trans women has been associated with a 4-times higher incidence of meningioma when compared to a cisgender female reference population (9). The true incidence is likely to be underestimated and there are no universally accepted meningioma screening guidelines for trans patients receiving CPA.

Despite meningioma being documented as a very rare adverse effect, we herein report 2 cases of giant intracranial meningioma occurring in patients receiving CPA, alerting us to the real-world risk of these tumors.

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Case Presentation

Patient 1

A 66-year-old trans woman presented to the emergency department in a postictal state after a first seizure. No focal neurological signs were observed, though a superficial eyebrow laceration was noted from a presumed head strike.

She commenced GAHT 20 years earlier; initially the oral contraceptive pill (CPA 2 mg/ethinylestradiol 35 mcg) for 3 years, after which her primary care provider prescribed CPA 50 mg and oral estradiol 2 mg daily. At presentation, she was taking CPA 100 mg daily (dose increased approximately 8 years prior) and oral estradiol 4 mg daily.

Her medical history included Asperger syndrome, depression (paroxetine 60 mg daily), and dyslipidemia (rosuvastatin 5 mg daily). There was a family history of malignancy in her siblings including lung, colorectal, and cervical cancer, although no meningioma. There was no previous cranial irradiation and no known hereditary syndromes associated with meningioma.

Patient 2

A 35-year-old trans woman presented to the emergency department with persistent headache and transient right-sided vision loss.

She commenced GAHT 5 years prior. She had tried various estradiol formulations, including oral, transdermal, and implants; her last implant was inserted 2 years ago. She initially commenced CPA 25 mg daily, although at presentation she was taking 12.5 mg daily.

Her medical history included anxiety, depression, autism spectrum disorder, and vitamin D deficiency (cholecalciferol 1000 IU daily). There was no personal history of cranial irradiation and no family history of malignancy or hereditary syndromes associated with meningioma.

Diagnostic Assessment

Patient 1

Computed tomography (CT) showed multiple enhancing extra-axial lesions, the largest measuring $52 \times 40 \times 50$ mm in the right frontal lobe, and 4 smaller right frontal lesions (largest $29 \times 22 \times 20$ mm). Magnetic resonance imaging (MRI) demonstrated multiple durally based enhancing lesions, in keeping with meningiomas, with associated midline shift and vasogenic edema (Fig. 1).

Blood specimens collected 5 days after estradiol and CPA cessation demonstrated a liquid chromatography–tandem mass spectrometry (LC-MS/MS) estradiol concentration of 110 pmol/L (30 pg/mL) (target range: 250-600 pmol/L; 68.1-163.4 pg/mL (11)) and total testosterone concentration of 2.4 nmol/L (69.2 ng/dL) (target range: < 2.0 nmol/L; < 57.7 ng/dL (11)).

Patient 2

MRI demonstrated a right posterior temporal mass measuring $57 \times 46 \times 41$ mm. The durally based lesion was causing mass effect, with effacement of the ventricles and midline shift. The imaging characteristics were consistent with a giant meningioma (Fig. 2).

Bloods collected prior to admission revealed a serum estradiol concentration of 415 pmol/L (113 pg/mL) (target range: 250-600 pmol/L; 68.1-163.4 pg/mL) via immunoassay, and a total testosterone concentration of 0.8 nmol/L (23.1 ng/dL) (target range: <2.0 nmol/L;<57.7 ng/dL).

Treatment

Patient 1

CPA was ceased and oral estradiol withheld given the unknown receptor status of her tumors. She received dexamethasone 4 mg twice daily and levetiracetam 1000 mg twice daily.

She proceeded to stealth-guided craniotomy with en bloc resection of the largest right frontal lesion. Immunohistochemistry revealed widespread progesterone receptor staining (> 90% of tumor cells) and negative estrogen receptor staining. Ki67 proliferation fraction was $< 5\%$ in the most active areas, consistent with a WHO grade 1 meningioma.

A targeted glioma next-generation sequencing (NGS) panel was requested to evaluate for molecular features associated with aggressive behavior, as well as supplementary testing

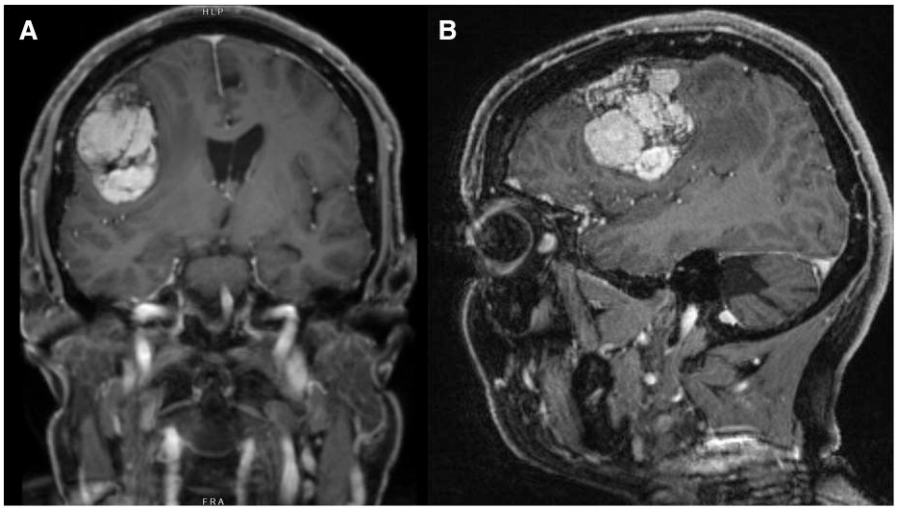

Figure 1. MRI brain demonstrating multiple right frontal lobe meningiomas (including one giant meningioma) with adjacent vasogenic edema and midline shift. A, Coronal view (T1-weighted); B, Sagittal view (T1-weighted).

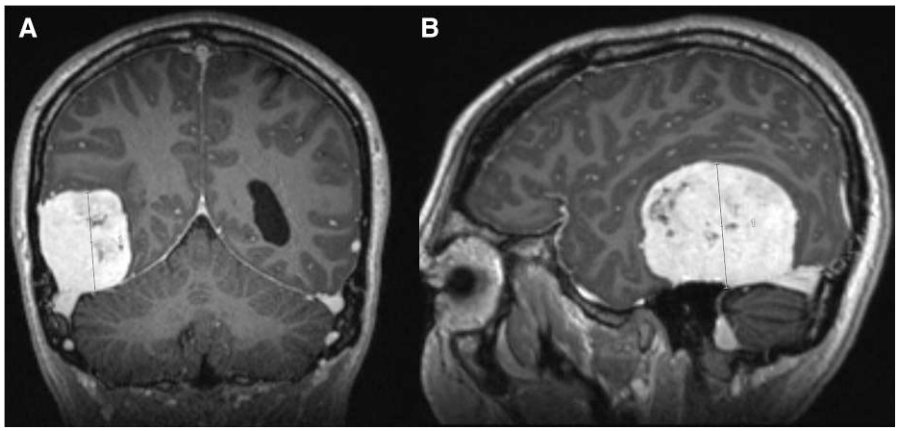

Figure 2. MRI brain demonstrating a right posterior temporal giant meningioma measuring 57 × 46 × 41 mm. A, Coronal view (T1-weighted); B, Sagittal view (T1-weighted).

for *PIK3CA* variants, which have been associated with progestin-associated meningioma. An oncogenic missense single nucleotide variant was detected (NM_006218.2*(PIK3CA):c.3140A > G(p.His1047Arg)*.

Patient 2

CPA was ceased and estradiol not prescribed given residual estradiol concentration of 415 pmol/L from her previous implant and the unknown receptor status of her tumor. She received dexamethasone 4 mg twice daily and levetiracetam 500 mg twice daily.

She underwent right temporal craniotomy with complete removal of the tumor. Immunohistochemistry showed widespread progesterone receptor staining (100% of tumor cells) and negative estrogen receptor staining. Ki67 proliferation fraction was < 5% in the most active areas, consistent with a WHO grade 1 meningioma. A targeted glioma NGS panel, with supplementary testing for *PIK3CA,* was negative.

Outcome and Follow-Up

Patient 1

The neuro-oncology multidisciplinary team recommended she remain off anti-androgen therapy with progestogenic activity. Due to recurrence of erections, endocrinology prescribed spironolactone 50 mg daily, which was uptitrated to 100 mg daily.

The patient was transferred to the brain injury rehabilitation unit due to residual postoperative deficits. Transdermal estradiol 0.1% (1 mg/g, 1 sachet daily) was prescribed once she was mobilizing independently. Improvements in language, physical, and cognitive functioning led to discharge 6 weeks later. Serum estradiol measured prior to discharge was 140 pmol/L (38.1 pg/mL) and total testosterone was 5.3 nmol/L (152.9 ng/dL).

Repeat MRI 5 months postoperatively showed resolution of mass effect and edema; the remaining meningiomas are stable in size (largest 32 mm).

Patient 2

The patient had an uncomplicated postoperative recovery and awaited histopathology results before recommencing GAHT. She was reviewed by endocrinology as an outpatient and histopathology results discussed; her preference was to commence spironolactone and remain off estradiol due to previous mood disturbance. She continues on spironolactone 100 mg daily and is planning orchiectomy.

In the absence of estradiol, she has been advised to ensure adequate dietary calcium intake, continue cholecalciferol, and engage in weight-bearing exercise. There is consideration for trialing low-dose estradiol for bone protection in the future.

Repeat MRI 6 months postoperatively showed resolution of mass effect and edema; no new lesions were demonstrated.

Discussion

The first signal of an association between prolonged high-dose CPA therapy and meningioma development in the trans population was reported in 2007 (12). A dose-effect relationship has been documented, particularly with high-dose CPA (> 50 mg/day) (13, 14); however, the dose below which CPA use is safe has yet to be determined. Cumulative CPA doses greater than 60 grams have been associated with a > 20-fold risk of developing meningioma in trans women (compared to controls), a risk that persists 12 months after CPA cessation (5).

A recent systematic review including 12 trans individuals who developed meningioma(s) while taking CPA reported the most frequent doses used were 50 to 100 mg daily, median age at presentation was 48 years, and median duration of use was 9.5 years (2). It is not documented how many were giant meningiomas, although 10 of 12 patients proceeded to surgery, and CPA was ceased in only 7 patients.

Notably, patient 1 was on high-dose CPA (≥ 50 mg) for almost 20 years and presented with multiple meningiomas (including one giant meningioma), whereas patient 2 was on lower dose CPA (≤ 25 mg) and presented with a giant meningioma after only 5 years of exposure. We therefore sought to evaluate other potential predisposing factors that may have increased our patients' risk.

Variants in *PIK3CA* and activation of the PI3K/AKT pathway have previously been observed in high-grade meningiomas (16); an increased frequency of *PIK3CA* variants have also been observed in progestin-associated meningiomas compared to those arising in the absence of progestogen therapy (15). We assessed for the presence of *PIK3CA* variants in

both patients; patient 1, who had multiple meningiomas, was found to carry an oncogenic missense variant in *PIK3CA*. Further studies into the role of *PIK3CA* variants in progestin-associated meningioma pathogenesis are required and may assist in predicting which patients are at risk of developing this adverse effect.

CPA cessation may be an appropriate strategy when surgery is not imminently required (2). Rapid meningioma regression and/or stabilization has been documented after CPA withdrawal (17, 18); however, this was not appropriate in our patients with neurological compromise. If CPA is chosen as anti-androgen therapy, the lowest possible dose should be used to maintain adequate testosterone suppression. Daily doses of 10 to 12.5 mg effectively lower testosterone, with fewer adverse effects (10, 19). In the absence of contraindications, spironolactone remains a suitable alternative anti-androgen and has not been associated with meningioma in either the cisgender or the trans population. Other less commonly prescribed anti-androgens include nonsteroidal anti-androgens (eg, bicalutamide) or gonadotropin-releasing hormone (GnRH) analogues (eg, leuprolide) (7). Micronized progesterone is also commonly prescribed in feminizing GAHT regimens but has not been associated with an increased risk of meningioma (20).

There is no consensus regarding MRI screening and/or surveillance in trans patients taking CPA. Based on the results of recent French pharmacovigilance studies, some groups have mandated annual MRI screening for patients taking doses of 50 to 100 mg (21). The cost-benefit analysis of routine MRI surveillance requires further evaluation, especially given that patient 2 developed meningioma with low cumulative CPA exposure. We recommend that patients are counseled on potential adverse effects of CPA (including meningioma) and clinicians remain vigilant for the development of neurological signs and symptoms that should prompt further evaluation with MRI.

Learning Points

- A dose-response association has been observed for cyproterone-associated meningioma, particularly with long-term exposure to doses ≥ 50 mg daily.
- Clinicians should be aware that cyproterone-associated meningioma can occur even with low-dose, shorter duration exposure.
- *PIK3CA* variants may play a role in the pathogenesis of progestin-associated meningioma, although this requires further evaluation.
- The lowest dose of CPA that maintains adequate testosterone suppression should be used, and alternative anti-androgens should be considered where appropriate.
- Clinicians should remain vigilant for neurological symptoms in patients receiving CPA and have a low threshold to undertake MRI.

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Contributors

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Informed Patient Consent for Publication

Signed informed consent was obtained directly from both patients.

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