

Meningioma: The Unusual Growth in a Transsexual Patient after Estrogen-Progesterone Therapy

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Introduction

The frequency of meningioma is nearly twice as high in females as in males [1]. This difference in incidence is partly explained by molecular and immunohistochemical studies' indicating that meningioma is sensitive to hormones. Approximately 70% of meningiomas express progesterone receptors and 30% express estrogen receptors [2-4]. It has also been observed that meningioma cells tend to proliferate when exposed to estrogen and progesterone [4].

Although cross-sex hormone treatment is an important component of medical treatment of transsexual patients, several adverse effects are associated with its use, such as osteoporosis, cardiovascular disease, hormone-dependent tumors (e.g., lactotroph adenomas), breast and prostate carcinomas. Specifically, research on Hormone Replacement Therapy (HRT) indicates that the risk of developing meningioma may be higher in transsexual patients due to relatively high doses of sex hormones [5,6]

In this article, we report a case of meningioma in a male-to-female transsexual patient undergoing HRT and propose that exposure to estradiol may have promoted fast meningioma tumor cell growth in an unusual manner. Thus, we hypothesize that the risk of developing a hormone-dependent tumor such as meningioma should be taken into account when evaluating potential candidates and examining patients undergoing male-to-female HRT.

Case Report

A 56-year-old male-to-female transsexual patient reported progressive severe left parietal headache during the previous

1.5 years. The neurological exam detected no abnormalities, but a review of clinical history revealed that the patient had been treated with Progynova (containing 2 g estradiol) for 8 years as well as cyproterone acetate, an anti-androgenic drug with semi-progesterone effects.

An initial Magnetic Resonance Imaging (MRI) exam in April 2011 showed positive evidence of a temporopolar meningioma (Figure 1). Consequently, the physician ordered the withdrawal of all hormonal medication. However, the patient, out of concern about losing female phenotype, continued to take Progynova.

A follow-up MRI occurring 6 months later showed that the temporal mass had unexpectedly increased in volume (Figure 2, Table 1). Therefore, the tumor was completely respected without any complication. Histopathology showed a transitional meningioma (WHO grade I) that was progesterone receptor-positive and estrogen receptor-negative (Figure 3).

Discussion

Cross-sex hormonal therapy is a fundamental component of

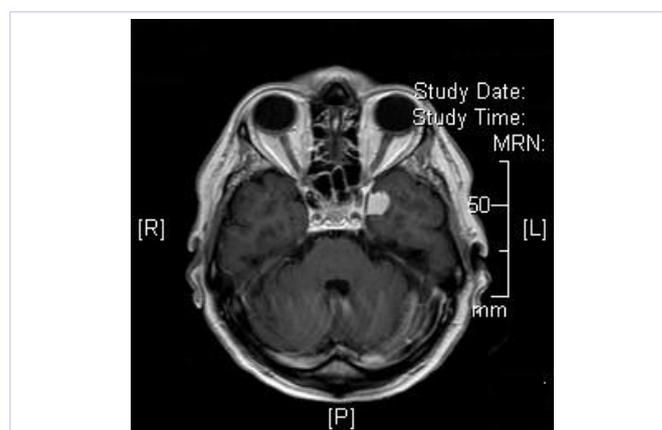


Figure 1: Initial MRI on April 2011 showing left Temporopolar Meningioma.

the endocrine regimen recommended for transsexual patients, but several studies associate HRT with a higher risk of developing intracranial meningioma (Table 2) [7-9]. Indeed, current endocrinological practice, the presence of pituitary adenomas contraindicates HRT and indicates that prolactin levels should be routinely monitored in male-to-female transsexuals [8,10].

More detailed molecular and immunohistochemical research provides evidence that meningiomas are hormone-sensitive tumors, with 70% of cells expressing progesterone receptors and around 30% expressing estrogen receptors [2-4]. Many of these studies also report that human meningioma cells proliferate when exposed to progesterone and estrogen [4]. Most meningiomas express functional progesterone rather than estrogen receptors [1,11] and show growth during the progesterone-predominant luteal phase [12].

Other studies have investigated the effects of estradiol treatment on progesterone receptors. Estradiol up-regulates progesterone receptors through α -estradiol receptors and can also stimulate hypothalamic progesterone receptors in the Medial Pre optic Nucleus (MPN) [13]. Some studies show that estradiol plays an important role in the ontogenic expression of progesterone receptors during postnatal uterine maturation in rats [14]. However, another study investigated the functionality of progesterone or estradiol receptors using polymerase chain reaction and provided evidence of a non-functional progesterone receptor *in vitro* [15].

Table 2: The summary of three cases of unusual meningioma's growth in transsexual patients after Estrogen-Progesterone Therapy (MTF: Male to Female, PR: Progesterone receptor, ER: Estrogen Receptor).

Case Report	Medication	Considerations
Gazzeri et al, 2007 [8] NEJM	Ethinyl Estradiol (100 microgram/day) & Cyproterone acetate (100 mg/d)	Frontobasal Meningioma ER - Ki-67 index of 5% MIB-1 index of 3.4 %
Deipolyi et al, 2010 [7] Journal of clinical Neuroscience	Estradiol 0.1 mg biweekly patches for more than 10 years	Left Occipital mass PR + ER -
Cebula et al, 2010 [9] Acta Neurochirurgie	Discontinuation of Cyproterone acetate	Regression of the left temporal meningioma after discontinuation of Cyproterone acetate

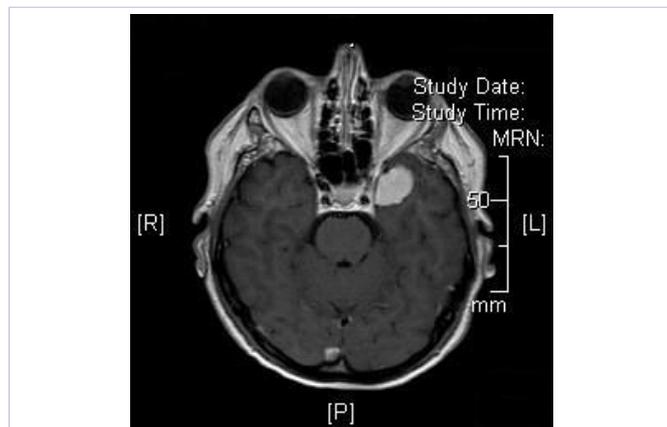


Figure 2: Six months later another MRI showing that the temporal mass had unexpectedly increased in volume.

Table 1: The rate of tumor growth 6 month after first MRI examination considering the natural history of meningioma.

Tumor Growth in first Examination	Tumor growth in second examination after 6 months
12×21×11mm [§]	22×26×20mm
The tumor growth in our patient: 10×5×9mm/6 month	
The average of tumor growth in patients without any hormonal usage: 4mm/year (18)	

[§]Tumor growth defined as a the greatest distance of tumor border from dura in coronal, axial and sagittal plane

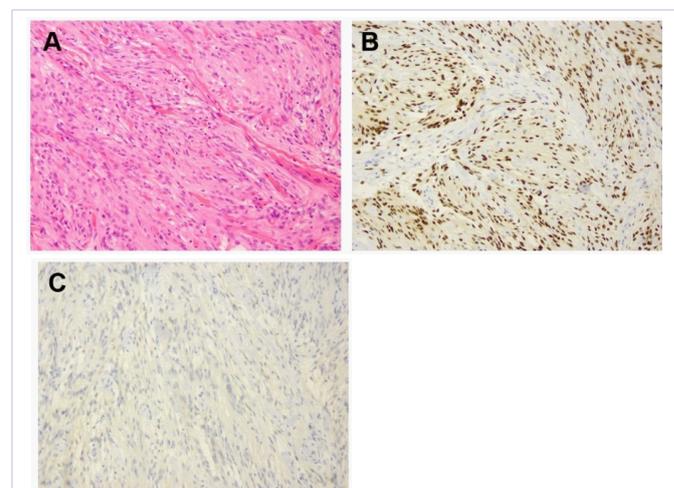


Figure 3: (A) Haematoxylin/eosin staining of the meningioma. (B) Strong expression of progesterone receptor in the nucleus of tumour cells. (C) Lack of estrogen receptor expression in tumour cells.

In experiments performed in rats during their growth phase, males expressed high levels of progesterone receptors in the MPN, whereas females had virtually no progesterone receptors, suggesting that exposure to estradiol has sex-dependent effects. The same study also found that the expression of progesterone receptors in the adult ventromedial nucleus depends on estradiol. Therefore, regulation of progesterone receptor expression through estradiol depends on age, sex, and brain region [16].

Most studies suggest that progesterone may contribute to meningioma pathogenesis, and trials of anti-progesterone treatment for inoperable meningiomas have shown excellent results. As a result, anti-progesterone drugs and the discontinuation of synthetic progesterone have been shown to inhibit meningioma cell growth, and the discontinuation of cyproterone acetate induces an abrupt regression of the tumor [17]. Accordingly, anti-progesterone therapy (e.g., Mifepristone, RU486) shows promise as a hormonal treatment for sphenoid ridge meningioma [18].

Table 3: The mechanism of medical effect on meningioma growth in our patient.

Medication	Mechanism 1	Mechanism 2
Progynova	Estrogen effect (Estradiol valerate)	----- -----
Ciproterone Acetat	Antiandrogenic effect	Semi progesterone effect

Despite the presence of progesterone-positive receptors and a low grade tumor in our patient, we consider that the contraindicated use of estradiol by the patient may have contributed to the unusually fast tumor growth. The tumor in our patient was progesterone receptor-positive and estrogen receptor-negative (Figure 3). However, the patient had been treated with Progynova containing 2 g estradiol and Cyproteron acetate, which is an anti-androgenic drug and has semi-progesterone effects (Table 3). In reviewing the literature, we found studies that examined the effects of estradiol on progesterone receptors experimentally. This literature indicates that estradiol up-regulates estrogen and progesterone receptors [13] and can induce expression of hypothalamic progesterone receptors [19]. As a result, we believe that the indirect effect of estrogen on progesterone receptors (i.e., up-regulation of progesterone receptors in the tumor and hypothalamus) changed the natural history of the meningioma and enhanced tumor growth in our patient.

The average annual growth rate for most meningiomas is about 4 mm per year [20]. In our case, the tumor grew 10 mm in 6 months (Table 1). Thus, despite immunohistochemical evidence that the meningioma was progesterone receptor-positive and estrogen receptor-negative, we propose that estradiol may have an effect on meningioma growth (Table 3).

Given that the prevalence of meningioma in U.S. men is 5:100,000 and the prevalence of male-to-female transsexuals is almost 1:10,000, the probability of an incidental meningioma in male-to-female transsexuals is about 1:200,000,000. This suggests that such an occurrence may not be coincidental [7]. Hence, in male-to-female transsexual patients undergoing HRT who are found to have a meningioma, the cessation of all sex hormones, not only progesterone's, is advised.

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